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ORIGINAL

THIRD PROGRESS REPORT
1978-1979

COMPLETED
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The United States—Japan Cooperative Cancer Research Program

U.S. - JAPAN COOPERATIVE CANCER RESEARCH PROGRAM
N.C.I. - J.S.P.S.

THIRD PROGRESS REPORT
1978-1979
The United States—Japan Cooperative Cancer Research Program

March 1979

Sponsors:
Japan Society for the Promotion of Science
and The National Cancer Institute

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Preface

It is our distinct honor and pleasure to submit the United States-Japan Cooperative Cancer Research Program Progress Report for 1978 to the Director of the National Cancer Institute (NCI) and the President of the Japan Society for the Promotion of Science (JSPS). The first and second reports covered the years 1974 to 1975 and 1976 to 1977. Together, these reports present the significant progress that has been made since the initial Agreement was signed on May 14, 1974, and bring us into the fifth and final year of the initial Agreement.

The purposes of the initial Agreement were threefold: (1) to sponsor scientific seminars to exchange information; (2) to support the exchange of scientists; and (3) to exchange materials and information to facilitate research of common interest. We believe these purposes to be more valid now than when they were conceived. They are all directed toward communication among scientists of different cultural backgrounds and wide geographic separation. Yet these purposes share a common bond in their fight against a dread disease shared by both countries. It is ironic that as the world "grows smaller" communication seems to be more difficult. However, communication is the heart of common problem solving among people of a single country, let alone two or more countries. We believe that great progress has been made during the past five years of the U.S.-Japan Joint Agreement in Cancer Research. Although the numbers of seminars, meetings, scientific workshops, scientist exchanges, and material exchanges speak well for the progress of the Program, they do not

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tell the whole story. What is not adequately conveyed in the numbers, or in the scientific progress, is the deep feeling of mutual respect among individuals from both countries that has evolved during the past five years. In sharing science, we also shared cultures and individual feelings. We made lasting friendships. In so doing, we not only contributed to science but, we believe, we also contributed to world peace. A world free of cancer should also be a world at peace.

The conclusion of the first phase of the initial formal Agreement provides us with five years upon which to reflect and learn in anticipation of a renewed agreement. We should strive to make future years even more productive. The next year will provide an opportunity to strengthen our combined efforts based on changing emphasis in the field of cancer research. Emphasis has shifted toward epidemiology and prevention, chemicals and their contribution to environmental carcinogenesis, nutrition and its role in cancer prevention, and combined modality treatment for some of the more common types of cancer afflicting all peoples. This change in emphasis reflects the fact that the ultimate control of cancer lies either in its reduced incidence through prevention or in its reduced mortality through effective treatment. In the coming years, some streamlining of our current program areas may be desirable. This does not necessarily imply less emphasis in any area, but rather a heightened emphasis in some areas. At certain critical points in time, change is healthy. It reflects progress. We must strive to maintain our strengths of the past while at the same time improving our ability to have an even more productive Program for the future.

We would like to give special recognition to Dr. Frank J. Rauscher, Jr., former Director, National Cancer Institute, for his involvement in the initiation and the enthusiastic support of the Program.

Dr. Gregory T. O'Conor, Director, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), was instrumental in initiating this Program. We gratefully express our appreciation to Dr. O'Conor for the interest and moral support he has provided during his tenure as the Associate Director for International Affairs, NCI.

We gratefully acknowledge Mr. Genkichi Hara and Mr. Kichimasa Soda for enthusiastic support of the Program during their tenures as Head of the Science Department, Japan Society for the Promotion of Science.

Since 1974, Dr. Arthur C. Upton has played an important role in the Program as the United States Program Coordinator for Chemical Carcinogenesis. We would like to extend our warmest congratulations to Dr. Upton upon his appointment as the Director of the National Cancer Institute and express our deep appreciation for his continuing support.

We especially wish to acknowledge the diligent work of the Joint NCI-JSPS Scientific Group and each of the Program Area Coordinators.

We are also very grateful for the special efforts and the endeavors of Mr. Nagahide Onozawa, Mr. Iwao Abe, Mrs. JoAnne W. Day, Mrs. Yuko K. Furukawa, and Dr. Robert R. Omata.

Guy R. Newell, M.D.

Haruo Sugano, M.D.

Co-Chairmen, U.S.-Japan Cooperative
Cancer Research Agreement

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INTRODUCTION

INTRODUCTION

The first five-year period of the U.S.-Japan Cooperative Cancer Research Program, which began in May 1974, has accomplished the general mission and the original purposes and objectives of the Program as framed by the original organizers. This Third Progress Report provides information on accomplishments made during the period April 1978 through March 1979, and terminates the first phase of the Program.

The Program Area Coordinators have also provided summaries of the activities sponsored by each of the program areas during the five-year period. Special recognition should be given to the Program Area Coordinators and to the numerous Japanese and American scientists who so generously contributed their time, effort, and cooperation toward the great success of this Program. Special acknowledgement is given to the staff members of the Japan Society for the Promotion of Science (JSPS) and the National Cancer Institute (NCI), who devoted a great deal of their effort and time toward the Program. We also wish to acknowledge the assistance of Mrs. Jean Cross and Ms. Joyce Douglass.

As joint editors of this Progress Report, we wish to express our gratitude to all of the Program Area Coordinators for the untiring effort, enthusiasm, and dedication they gave to the Program. It is our hope that they have been able to gain as much as they have given to the Program. We are hopeful that the friendly relationships developed with the help of the Program will long endure and continue to contribute toward scientific progress between the scientists of Japan and the United States.

Kichimasa Soda
Head, Science Department
Japan Society for the Promotion of Science

Robert R. Omata, Ph.D.
Executive Secretary
U.S.-Japan Cooperative
Cancer Research Program
Office of International Affairs
National Cancer Institute

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CHEMICAL CARCINOGENESIS PROGRAM AREA REPORT

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Program Coordinators:
Dr. Takashi Sugimura
Dr. I. Bernard Weinstein

CHEMICAL CARCINOGENESIS PROGRAM AREA REPORT

September 1977 to March 1979

Administrative Report and Scientific Summary

Progress continues to be made in this program area through three basic groups of activities: Meetings, Seminars, and Conferences; Exchange of Scientists; and Exchange of Materials.

MEETINGS, SEMINARS, AND CONFERENCES

During this reporting period, a conference on the "Role of DNA Repair and Misrepair in Radiation and Chemical Carcinogenesis" was held in Kyoto, Japan, from December 12 to 14, 1977. This meeting was organized by Drs. A.C. Upton, T. Sugimura, R. Setlow, W. Troll, and I.B. Weinstein, and was held jointly with the First Radiation Biology Center International Symposium entitled "Molecular Mechanisms and Genetic Factors in Radiation Carcinogenesis." This second meeting was held in Kyoto, Japan, on December 15, 1977, and was organized by Drs. A.C. Upton, T. Sugahara, and H. Takebe.

The joint scheduling of these two meetings increased the number of speakers that could be invited, thus including several outstanding scientists from Japan, the United States, England, and Europe, with a total of about 60 participants. The names of the invited speakers and the programs of both meetings follow this Program Area Report.

There is increasing recognition of the importance of DNA repair mechanisms in the carcinogenic process. Genetic and perhaps metabolic variations in the efficiency and fidelity of cellular DNA repair in response to damage inflicted by environmental carcinogens and mutagens are extremely important determinants of host susceptibility. Hereditary diseases like *xeroderma pigmentosum* readily demonstrate this principle. The symposia spanned a broad range of topics including human medical genetics, cytogenetics, mutagenesis and carcinogenesis, radiation biology, interactions with viruses, and biochemical, enzymatic, and molecular studies of DNA repair. Recent advances in research on the human heritable disorders *xeroderma pigmentosum*, *xeroderma pigmentosum* varients, Fanconi's anemia, ataxia telangiectasia, and Bloom's syndrome were reviewed. The emerging results provide clues to the complexity of DNA repair mechanisms in mammalian cells. For reasons that are not known, numerous cases of *xeroderma pigmentosum* have been found in Japan; cell lines established from these cases are proving to be extremely useful in research studies. Drs. Maher and McCormick (Michigan State University) presented studies with *xeroderma pigmentosum* cell cultures indicating that they are more susceptible to mutagenesis by ultraviolet light and by certain chemical carcinogens than are normal cells.

Encouraging progress in the identification and purification of specific enzymes involved in DNA repair was also presented. Dr. Mutsuo Sekiguchi, Kyushu University, reported on the purification of a T4 phage enzyme that specifically excises thymine dimers. He also described an N-glycosidase enzyme that excises uracil residues from DNA. Dr. Stuart Linn, University of California at Berkeley, described purification of a human apurinic endonuclease. He also described preliminary experiments suggesting the existence of a novel "insertase" enzyme that re-inserts base residues into apurinic sites in DNA. Dr. M. Radman, Brussels; Dr. S.G. Sedgwick, National Institute for Medical Research, London; and Dr. W. Troll, New York University, described the "SOS" mechanisms involved in phage activation and mutagenesis in bacteria. Evidence was presented that these responses to DNA damage, particularly bulky lesions in DNA, involve induction of an "error-prone" DNA polymerase and the action of proteases.

Dr. Sugimura presented recent results of investigations in Japan indicating that the protease inhibitor "elastatinal" inhibits mutagenesis in *S. typhimurium* and that the tryptophane pyrolysis products norharman and harman enhance mutagenesis in this bacterial system. He also reported that elastatinal inhibits *in vitro* transformation of Syrian hamster embryo cultures by MNNG. Evidence that the protease inhibitor antipain inhibits mutagenesis in *E. coli* was presented by Ryo H. Ichikawa and Sohei Kondo (Osaka). Dr. Troll described exciting studies indicating that proteases are involved in the inactivation of repressors in bacterial systems. He reviewed evidence that proteases may also play an important role in carcinogenesis. Dr. I. Bernard Weinstein, Columbia University, described the types of covalent adducts formed between DNA and activated forms of Benzo(a)pyrene and DMBA. He reviewed recent evidence that tumor promoters induce a number of phenotypic properties that resemble those seen in tumor cells and also inhibit cellular differentiation. Additional papers dealt with chromosomal changes and interactions between radiation, chemical carcinogens, and oncogenic viruses. The meetings ended with the presentation of a paper by Dr. H.P. Klinger, Albert Einstein College of Medicine, New York, describing the suppression of tumorigenicity in somatic cell hybrids and associated chromosomal correlations.

Participants from Japan and abroad found these two meetings extremely stimulating and productive. There is no doubt that the information exchanged, the collaborations established, and the warm friendships made in Kyoto will greatly enhance advances in this important area of cancer research.

At a second conference sponsored by the U.S.-Japan Cooperative Cancer Research Program held at the East-West Center, University of Hawaii, March 26 to 28, 1979, 17 researchers met to discuss "Gene Derepression and Host-Tumor Relationships in Carcinogenesis." Chairmen at this conference were Drs. S. Weinhouse, T. Ono, and A. Ichihara. The agenda and minutes of the meeting follow this Program Area Report.

Exchange of Scientists

A very productive aspect of the Chemical Carcinogenesis Program Area has been that of scientist exchange. In the period covered by this Report, the following scientists visited their counterparts:

1. Dr. Yutaka Tsukada, from Hokkaido University School of Medicine, visited Dr. Van R. Potter's laboratory at the McArdle Laboratory, University of Wisconsin. Dr. Tsukada conducted studies on the induction of AFP synthesis and secretion in H35 hepatoma cells by dexamethasone and the effects of feeding alphanaphthylisothiocynate on AFP synthesis and gamma glutaml-transpeptidase.

2. Dr. Hiroyasu Esumi, National Cancer Center Research Institute, Tokyo, visited the laboratories of Dr. W. Troll, New York University and Dr. L. Greenbaum, Columbia University. During August and September 1978, Dr. Esumi performed collaborative studies on the effects of tumor promoters on differentiation and on protease action. During his visit, he also participated in the Gordon Cancer Conference in August 1978, where he presented a paper on his research studies. In studies conducted with Dr. Troll at the Woods Hole Marine Biology Laboratory, he found that a phorbol ester tumor promoter inhibits sea urchin development.

   In addition, Dr. Esumi and Dr. L. Greenbaum continued their studies on the role of proteases in ascites fluid accumulation.

3. Dr. Kohtaro Koyama, National Cancer Center Research Institute, Tokyo, visited the Division of Biochemical Oncology, Fred Hutchinson Cancer Research Center, University of Washington, Seattle (host: Dr. Sen'ichiro Hakomori, September 1, 1977 to February 28, 1978). He analyzed the cell surface proteins, carbohydrates, and glycolipids in membranes of several variants of fibrosarcoma cell lines.

4. Dr. Lowell Greenbaum, Columbia University, visited Dr. T. Sugimura and other scientists in Japan for collaborative studies on the role of proteases in tumor ascites accumulation and prevention of ascites formation by protease inhibitors.

5. Dr. A. Hsie, Oak Ridge National Laboratories, visited Dr. T. Sugimura and his colleagues to discuss *in vitro* studies on mammalian cell mutagenesis and assays for carcinogens using this system. His visit assisted in the establishment of the CHO mutagenesis assay in Japanese laboratories.

6. Dr. Veronica Maher participated in two meetings on DNA repair held in Kyoto in December 1977. Dr. Maher then visited several laboratories in Japan where she and Dr. Justin McCormick discussed studies that they have done demonstrating increased sensitivity to mutagenesis in *xeroderma pigmentosum* cultures and more general aspects of DNA damage and repair.

7. Dr. I. Bernard Weinstein, Columbia University, New York, was an exchange scientist in Japan from December 5 to 24, 1977. He participated in the U.S.-Japan Cancer Seminar on the "Role of DNA Repair and Misrepair in Radiation and Chemical Carcinogenesis," for which he was co-organizer, and the First Radiation Biology Center International Symposium on "Molecular Mechanisms and Genetic Factors in Radiation Carcinogenesis" held in Kyoto on December 12 to 14 and December 15, 1977, respectively. During his stay in Japan, he presented research seminars on the subject of "Structural and Functional Changes in Nucleic Acids Modified by Activated Forms of Benzo (a) pyrene" and "Studies on the Mechanism of Action of Tumor Promoters in Cell Culture." Seminars on these subjects were presented at the two meetings in Kyoto described above, and at the National Cancer Research Center in Tokyo, the Cancer Institute in Tokyo, the Institute of Medical Sciences in Tokyo, and the University of Tokushima. He also visited numerous research laboratories in Japan to learn details of research projects in the areas of carcinogenesis and to discuss possible areas of collaborative research. The scientists with whom he had detailed discussions included Drs. T. Sugimura, S. Nishimura, Y. Kuchino, H. Kasai, N. Nemoto, S. Takayama, M. Muramatsu, H. Sugano, I. Matsushima, I. Hirono, N. Yamaguchi, H. Shimojo, Y. Ikawa and T. Yamamoto in Tokyo; A. Ichihara and S. Ohtsuka in Tokushima; and S. Kondo, T. Sugahara, H. Takebe, M. Sekiguchi, and H. Yoshikura in Kyoto.

   Dr. Weinstein found considerable interest in recent cell culture studies in his own laboratory and other laboratories in the United States on the mechanism of action of tumor promoters. He has subsequently sent samples of phorbol esters and related macrocydic diterpenes to Dr. T. Sugimura and his colleagues for studies on myeloid cell differentiation; to Dr. Y. Ikawa for studies on the transformation of chick embryo fibroblasts by avian sarcoma virus; to Dr. A. Ichihara for studies on liver isozymes; and to Dr. T. Sugiyama, Department of Pathology, Kobe University, for studies on erythroid differentiation in DMBA induced erythroleukemia cell lines.

   The possible roles of natural products in tumor promotion were discussed in detail with Dr. Iwao Hirono at the Institute of Medical Sciences (IMS) in Tokyo and Dr. Hirata Hoshimasa, Department of Chemistry, Nagoya University. This subject could develop into a future area for productive collaborative studies between Japanese and U.S. scientists.

EXCHANGE OF MATERIALS

An extremely valuable aspect of the U.S.-Japan Cooperative Cancer Research Program in the area of carcinogenesis has been the generous gift from Japanese scientists of several highly novel and specific protease inhibitors to researchers in the United States and elsewhere. Drs. Walter Troll and Bernard Weinstein have supervised the distribution of these compounds to over 65 U.S. scientists, as well as five scientists in the United Kingdom, three in Canada, two in West Germany, three in Israel, two in Belgium, and one scientist each in Switzerland, Poland, South Africa, and the U.S.S.R. The availability of these materials has made it possible to advance our understanding of the role of proteases in phage induction, in mutagenesis, and in the carcinogenic process itself. The results have been of major interest to the fields of bacterial genetics, mutagenesis, and carcinogenesis. The rapid advances in our understanding of the role of proteases in normal and abnormal growth would not have been possible without these inhibitors and the data on their properties so generously provided by the Japanese scientists.

The U.S.-Japan Cooperative Cancer Research Program has also greatly stimulated the exchange of information and materials between U.S. and Japanese scientists in the areas of carcinogenesis and tumor promotion. Dr. Sugimura's laboratory has obtained evidence that croton oil enhances the induction of gastric cancer in rats and that phorbol esters influence the maturation of leukemia cells in culture. Drs. Sugimura and Takayama participated in a Symposium on Tumor Promotion organized by Drs. I. Bernard Weinstein and Walter Troll at Cold Spring Harbor in May 1978. Other exchanges of materials and information related to tumor promoters are described above in the Exchange of Scientists section.

Current and Future Activities, 1978 to 1979

CONFERENCE UNDER DISCUSSION

The following topics are under consideration for future conferences:

Epidemiologic and Medical Applications of Computer Technology

Eukaryotic DNA Replication

Carcinogenesis Studies in Human Cells and Tissues

Metabolic Epidemiology—Dietary, Genetic, Hormonal Factors; Natural Carcinogens; Variations in Host Metabolism

Interactions Between Chemical Carcinogens and Oncogenic Viruses in Cancer Causation.

EXCHANGE OF SCIENTISTS

The following two American scientists recently visited Japanese colleagues:

Dr. Ernst Borek, University of Colorado, visited the National Cancer Center Research Institute, Tokyo, in March 1979. The hosts were Y. Kuchino and S. Nishimura.

Project Title: "Alterations in Modified Bases in Hepatoma Transfer RNAs"

Dr. Dezider Grunberger, Columbia University, visited the National Cancer Center Research Institute, Tokyo, in November 1978. This visit was hosted by S. Nishimura.

Project Title: "Structure Studies on Transfer RNAs in Tumor Cells and the Effects of Nutritional Factors"

EXCHANGE OF RESOURCES (tentative)

The following chemical substances are being considered for exchange between the United States and Japan:

Mutagens from amino acid pyrolysates discovered in Japan that may be potential carcinogens in cooked foods. To be provided by Dr. T. Sugimura and colleagues and distributed to American scientists with the assistance of Dr. Kakunaga, National Cancer Institute, Bethesda.

Activated forms of polycyclic aromatic hydrocarbons synthesized by American scientists.

Phorbol esters and related macrocyclic plant diterpene tumor promoters to be provided by American scientists.

Continued supply of protease inhibitors from Japanese scientists.

ETIOLOGY PROGRAM AREA

The following subject areas are under discussion for future collaborative efforts in this program area: Epidemiology, chemical and radiation carcinogenesis, viral carcinogenesis, genetics and molecular oncology.

United States and Japanese principal advisors in each of the above areas are being discussed.

OBJECTIVES

Beginning in 1979, the major objective of the Second Five-Year Cooperative Cancer Research Program in the Carcinogenesis Program Area is to "identify carcinogenic factors and clarify mechanisms with a view to providing a fundamental basis for the prevention of human cancer."

CONFERENCE REPORTS

6A

U.S.-Japan Cancer Seminar*

ROLE OF DNA REPAIR AND MISREPAIR IN RADIATION AND CHEMICAL CARCINOGENESIS

Kyoto Grand Hotel, Kyoto, Japan
December 12-14, 1977

AGENDA

Monday, December 12

9:00 a.m. Welcome
Dr. T. Sugahara

9:05 a.m. Opening Session
Dr. T. Sugahara—Chairperson

Opening Remarks
Dr. T. Sugimura

Introduction
Dr. I. B. Weinstein

Session 1: DNA Repair Defects in Hereditary Diseases with High Incidence of Cancer

Drs. H. Takebe and D. Bootsma—Co-Chairpersons

9:45 a.m. 1. Repair Defect and Chromosomal Sensitivity in *Xeroderma Pigmentosum*
Dr. M. S. Sasaki

10:15 a.m. Discussion

10:25 a.m. COFFEE BREAK

10:45 a.m. 2. Ataxia Telangiectasia: A Model Genetic Disorder Relating Radiogenic DNA Damage to Human Malignancy
Dr. M. C. Paterson

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*Sponsored by the National Cancer Institute (U.S.A.) and the Japan Society for the Promotion of Science; coordinated by Drs. A. C. Upton, I. B. Weinstein, and T. Sugimura.

Monday, December 12 (continued)

11:15 a.m.	Discussion	
11:25 a.m.	3.	Relationship between DNA Repair Defects and Skin Cancers in *Xeroderma Pigmentosum* **Dr. H. Takebe**
11:55 a.m.	Discussion	
12:05 p.m.	LUNCH	

Session 1: (continued)
Drs. Y. Fujiwara and V. M. Maher—Co-Chairpersons

1:15 p.m.	4.	Postreplication Repair in UV-irradiated *Xeroderma Pigmentosum* (XP) and its Variant Cells and Skin Carcinogenesis **Dr. Y. Fujiwara**
1:45 p.m.	Discussion	
1:55 p.m.	5.	Cell Killing and Mutation in Human Repair Defective Syndromes **Dr. C. F. Arlett**
2:25 p.m.	Discussion	
2:35 p.m.	6.	Biological Evidence that DNA Repair Processes in Normal Human Cells Act to Reduce the Lethal and Mutagenic Effects of Exposure to Carcinogens **Drs. V. M. Maher and J. J. McCormick**
3:05 p.m.	Discussion	
3:15 p.m.	COFFEE BREAK	
3:35 p.m.	7.	Enzymes that Recognize DNA Damages Induced by Ultraviolet Light and Certain Chemicals **Dr. M. Sekiguchi**
4:05 p.m.	Discussion	
4:15 p.m.	8.	Enzymes for the Repair of Apurinic/Apyrimidinic Sites in Human Cells **Dr. S. Linn**
4:45 p.m.	Discussion	

Tuesday, December 13

Session 2: Genetic and Epigenetic Factors in Radiation and Chemical Carcinogenesis

Drs. T. Sugimura and I. B. Weinstein—Co-Chairpersons

8:30 a.m.	9. DNA Damage and Cancer Production by 4-hydroxy-aminoquinoline-1-oxide (4HAQO) after Partial Pancreatectomy (p.p.) in Rats **Dr. Y. Konishi**
9:00 a.m.	Discussion
9:10 a.m.	10. Biological and Biochemical Effects of Various Carcinogens in Normal and XP Strains **Drs. J. J. McCormick and V. M. Maher**
9:40 a.m.	Discussion
9:50 a.m.	COFFEE BREAK
10:10 a.m.	11. Genetic and Epigenetic Factors in Chemical Carcinogenesis **Dr. I. B. Weinstein**
10:40 a.m.	Discussion
10:50 a.m.	12. Enhancement and Suppression of Mutagenesis **Dr. T. Sugimura**
11:20 a.m.	Discussion
11:30 a.m.	LUNCH
12:30 p.m.	Excursion

Wednesday, December 14

Session 2: (continued)

Drs. K. Yokoro and L. G. Lajtha—Co-Chairpersons

9:00 a.m.	13. Chemical Carcinogen Action and Repair at the Chromosomal Level **Dr. T. Sugiyama**
9:30 a.m.	Discussion

Wednesday, December 14 (continued)

9:40 a.m. 14. Induction of Endogenous Murine Leukemia Virus: Effect of Caffeine and Polycyclic Carbons
Dr. H. Yoshikura

10:10 a.m. Discussion

10:20 a.m. 15. Radiation Induction of Endogenous Murine Leukemia Virus *in vitro*: Effect of Antipain on the Induction Frequency. (Discussion Paper)
Dr. O. Niwa

10:30 a.m. Discussion

10:55 a.m. COFFEE BREAK

Session 3: Inducible Repair and Role of Misrepair in Carcinogenesis and Mutagenesis

Drs. M. Sekiguchi and S. Linn—Co-Chairpersons

11:15 a.m. 16. Post-replication Error-Prone Repair of DNA Damage
Dr. M. Radman

11:45 a.m. 17. Genetic Control of UV Mutagenesis in *Escherichia coli*. (Discussion Paper)
Dr. T. Kato

11:55 a.m. Discussion

12:10 p.m. LUNCH

1:15 p.m. 18. Error-Free and Error-Prone DNA Repair in *Escherichia coli*
Dr. S. Sedgwick

1:45 p.m. Discussion

Session 3: (continued)
Drs. S. Kondo and W. Troll—Co-Chairpersons

2:00 p.m. 19. Differential Antimutagenicities of Caffeine and Antipain (a Protease Inhibitor) in *Escherichia coli* Treated with Different Mutagens
Drs. Ryo H. Ichikawa and S. Kondo

Wednesday, December 14 (continued)

2:30 p.m.	Discussion
2:40 p.m.	20. Inhibition of Tumor Initiation by Protease Inhibitors **Dr. W. Troll**
3:10 p.m.	Discussion
3:20 p.m.	21. Caffeine Effects on Chemical Carcinogenesis **Dr. T. Nomura**
3:50 p.m.	Discussion

Closing Session

Dr. T. Sugimura—Chairperson

4:15 p.m.	Summary and Closing Remarks **Dr. T. Sugahara**
	General Discussion
4:55 p.m.	Adjournment

The First Radiation Biology Center International Symposium*

MOLECULAR MECHANISMS AND GENETIC FACTORS IN RADIATION CARCINOGENESIS

Kyoto Grand Hotel, Kyoto, Japan
December 15, 1977

AGENDA

Thursday, December 15

9:00 a.m. Opening Remarks
Dr. T. Sugahara

Session 1: Molecular and Cellular Aspects in Radiation Carcinogenesis

Drs. H. Tanooka and M. Radman—Co-Chairpersons

9:10 a.m. 1. A Review of the Mechanism(s) for Induction of Error-Prone Repair
Dr. S. Sedgwick

9:40 a.m. Discussion

9:50 a.m. 2. Persistence of Radiation-Induced Carcinogenic Damage in the Mouse Skin and its Modification by Caffeine
Drs. H. Hoshino and H. Tanooka

10:20 a.m. Discussion

10:30 a.m. COFFEE BREAK

10:50 a.m. 3. Radiation-Induced Salivary Gland Tumor
Dr. F. Hirose

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*Sponsored by the Radiation Biology Center, Kyoto University; organized by Drs. A. C. Upton, T. Sugahara, and H. Takebe.

December 15 (continued)

11:20 a.m.	Discussion
11:30 a.m.	4. On Cellular Aspects of Leukemogenesis **Dr. L. G. Lajtha**
12:00 noon	Discussion
12:10 p.m.	LUNCH

Session 2: Genetic Factors in Radiation Carcinogenesis

Drs. A. Tonomura and M. C. Paterson—Co-Chairpersons

1:20 p.m.	5. Chromosome Aberrations in General Population **Dr. A. Tonomura**
1:50 p.m.	Discussion
2:00 p.m.	6. Cell Killing and Mutation in Human Repair Defective Syndromes **Dr. C. F. Arlett**
2:30 p.m.	Discussion
2:40 p.m.	7. Repair of the Radiation-Induced Lethal and Mutational Damage in Cultured Chinese Hamster Cells **Dr. M. Horikawa**
3:10 p.m.	Discussion
3:20 p.m.	COFFEE BREAK
3:40 p.m.	8. Genetic Analysis of Mammalian Cells by Gene Transfer Systems **Dr. D. Bootsma**
4:10 p.m.	Discussion
4:20 p.m.	9. Suppression of Tumorigenecity in Somatic Cell Hybrids **Dr. H. P. Klinger**
4:50 p.m.	Discussion
5:00 p.m.	Closing Remarks **Dr. H. Takebe**

CONFERENCE ON GENE DEREPRESSION AND HOST-TUMOR RELATIONSHIPS IN CARCINOGENESIS

East West Center, Honolulu
March 26-28, 1979

AGENDA

Monday, March 26

1. Abnormal Gene Expression in Tumors

9:00 a.m. Is There Any Relationship between Arachidonic Acid Metabolism and Tumor Production?

Lawrence Levine, Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts

9:45 a.m. Chemistry and Expression of Alpha-Fetoprotein and Its Molecular Variants

Erkki Ruoslahti, Division of Immunology, City of Hope National Medical Center, Duarte, California

10:30 a.m. COFFEE BREAK

10:45 a.m. Reexpression and Modulation of Developmental Alkaline Phosphatases in Tumor Cells

William Fishman, La Jolla Cancer Research Foundation, La Jolla, California

11:30 a.m. Polypeptide Growth Factors Produced by Virus-transformed Cells and by Tumor Cells

Joseph DeLarco (and **George Todaro**), Laboratory of Viral Carcinogenesis, National Cancer Institute, Bethesda, Maryland

12:15 p.m. LUNCH

2:00 p.m. Gene Expression in Primary Cultured Rat Hepatocytes

Akira Ichihara, Institute of Enzyme Research, Tokushima University Medical School, Tokushima

Monday, March 26 (continued)

2:45 p.m. tRNA Transglycosylase from *E. Coli* and Rat Liver: Novel Mechanism of Post-Transcriptional Modification of tRNA, and Its Implication in the Detection of Under-Modified Unique tRNA Species in Tumor Tissues

Susumu Nishimura, National Cancer Center Research Institute, Tokyo

3:15 p.m. Ectopic Hormone Production in Human Tumors as an Abnormal Gene Expression

Hiro Imura, Kyoto University Medical School, Kyoto

Tuesday, March 27

2. Initiation and Promotion

9:00 a.m. Studies on the Mechanisms of Action of Tumor Promoters

I. B. Weinstein, Institute for Cancer Research, Columbia University, College of Physicians and Surgeons, New York, New York

9:45 a.m. Effects of Tumor Promoters on the Differentiation of Friend Leukemia Cells in Culture

Tetsuo Ono, Tokyo Metropolitan Institute for Medical Science, Tokyo

10:30 a.m. COFFEE BREAK

10:45 a.m. Naturally Occurring Genotoxic and Non-genotoxic Carcinogens

Takashi Sugimura, National Cancer Center Research Institute, Tokyo

11:30 a.m. Effects of Modifiers of Tumor Promotion on Differentiation of Leukemia Cells

Moto Hozumi, Saitama Cancer Research Center, Saitama

12:15 p.m LUNCH

3. Effects of Tumors on Host Metabolism

2:00 p.m. Alterations in the Enzymic Composition of Liver and Spleen in Response to Distant Neoplasms

Olga Greengard, Department of Pediatrics, Mount Sinai Medical Center, New York, New York

Tuesday, March 27 (continued)

2:45 p.m. Expression of the Fetal Isozyme of Pyruvate Kinase in Adult Non-neoplastic Liver

Kenneth H. Ibsen, Department of Biological Chemistry, California College of Medicine, University of California, Irvine, California

3:30 p.m. General discussion

Wednesday, March 28

3. **Effects of Tumors on Host Metabolism** (continued)

9:00 a.m. A Factor Responsible for Increase in Ornithine Decarboxylase Activity in the Liver of Tumor-bearing Mice: Partial Purification and Characterization

Takehiko Tanaka, Osaka University Medical School, Osaka

9:45 a.m. Effects of Tumor on Host Liver Nitrogen Metabolism

Sidney Weinhouse, Fels Research Institute, Temple Medical School, Philadelphia, Pennsylvania

10:30 a.m. DNA Synthesis in Tumor-bearing Rats: Thymidine Kinase-stimulating Factor

Setsuro Fujii, Institute of Protein Research, Osaka University Medical School, Osaka

MINUTES OF THE CONFERENCE ON GENE DEREPRESSION AND HOST-TUMOR RELATIONSHIPS IN CARCINOGENESIS

Honolulu, Hawaii

March 26 to 28, 1979

Evidence from several areas of biology points to abnormalities of gene regulation as a common feature underlying many of the diverse phenotypic properties associated with the induction and maintenance of the neoplastic state. At a conference sponsored by the U.S.-Japan Cooperative Cancer Research Program held at the East-West Center, University of Hawaii, 17 researchers met to discuss these topics. The program was divided into three main segments: abnormal gene expression in tumors; initiation and promotion; and effects of tumors on host metabolism.

Dr. Lawrence Levine, Brandeis University, pointed out that several tumors synthesize and excrete large amounts of prostaglandin E_2, and that prostaglandins and their metabolites are elevated in the plasma of tumor hosts. This is assumed to be responsible for hypercalcemia and bone-resorption. Dr. Levine found that a large number of carcinogens and promoters stimulate prostaglandin formation by activating phospholipase A, thereby releasing arachidonic acid, its precursor.

Dr. Alan Mufson, Columbia University, enlarged upon the role of arachidonic acid release and prostaglandin formation in tumor promoter activity. In contrast with carcinogens, which attach covalently to DNA, promoters are not mutagenic and their target is the cell membrane. At nanomolar concentrations, they alter cell morphology, alter cell surface components such as fucose-glycopeptides and LETS protein, increase saturation density, and increase production of plasminogen activator and ornithine decarboxylase. The same effects are enhanced in transformed cells. Phorbol esters and related tumor-promoting plant diterpenes reversibly inhibit cell differentiation, as demonstrated by a variety of experimental systems, and reduce binding of epidermal growth factor to tumor cells.

Dr. Tetsuo Ono, Tokyo Metropolitan Institute of Medical Science, described inhibitory effects of a variety of tumor promoters on differentiation of Friend erythroleukemia cells induced by hexamethylene bisacetamide. Urea, phorbol esters, deoxycholate, and Tween-60 either inhibited or increased the inhibitory effect of phorbol ester in this system. Carcinogens such as urethane, DMBA, 4-NQO, and saccharin, considered to be weak carcinogens as well as promoters, did not inhibit differentiation.

Using another experimental system, Dr. Moto Hozumi, Saitama Cancer Research Center, reported that the differentiation of a mouse myeloid leukemic (MI) cell line to macrophages and granulocytes was triggered by a variety of substances, including sera, ascitic fluid, saliva, urine, amniotic fluid, and various polynucleotides.

Differentiation of MI cells was also induced by inhibitors of promotion in mouse skin, such as glucocorticoides, some prostaglandins, cyclic AMP, poly I-poly C, interferon, and vitamin A. Differentiation induced by steroids was highly specific to certain structures, was dependent on binding to dexamethasone receptors, and was inhibited by low concentrations of phorbol esters and other tumor-promoting diterpenes.

Dr. Takashi Sugimura, National Cancer Center, Tokyo, provided another experimental system, the use of microbial species for detection of mutagenesis, to aid in the dissection of initiation and promotion. Among the striking findings reported were the discovery and chemical identification of new classes of highly potent carcinogens formed by pyrolysis of meat, fish, and individual amino acids such as tryptophan and glutamic acid. Dr. Sugimura classified tumorigenic agents as genotoxic (initiators) and non-genotoxic (promoters) and reported evidence of a novel concept: co-mutagenesis by two agents, neither of which is mutagenic individually.

One of the most striking examples of gene derepression in cancer is the expression of fetal gene products. Dr. Erkki Ruoslahti, City of Hope Medical Center, Duarte, California, described a new isolation method for α-feto-protein, a product of liver and germ cell neoplasms, based on use of interspecies cross-reactivity of antibody, to produce gram quantities. This protein shows amino acid sequence homology with albumin as well as similarities in binding fatty acids; but it contains carbohydrate, the amount and composition of which may differ according to its source. The tumor form appears to resemble that of the yolk sac rather than that of the liver. Dr. Ruoslahti made the important point that AFP is produced in non-neoplastic hepatoproliferative conditions such as cirrhosis, hepatitis, partial hepatectomy, early premalignant effects of carcinogens, and in certain hereditary conditions, such as tyrosinemia and ataxia telangiectasia. It also persists as a hereditary trait in BALB/C/J mice.

According to Dr. William Fishman, La Jolla Cancer Research Foundation, California, the developmental expression of the many alkaline phosphatase isozymes follows a definite pattern, which is re-expressed as an oncodevelopmental feature in specific tumors.

Both Drs. Ruoslahti and Fishman dwelt on the the expression of γ-glutamyl peptidotransferase, an enzyme rapidly assuming importance as an early marker of neoplasia. According to Dr. Ruoslahti, the activity of this enzyme is not correlated closely with AFP production. Dr. Fishman, who found this enzyme in lung and colon tumors, emphasized its embryonal expression in testes, blastocysts, and trophoblasts.

Dr. Susumu Nishimura, National Cancer Center, Tokyo, described another example of abnormal gene regulation resulting in novel isoprotein species in tumors, namely isoaccepting tRNAs, which have Q base adjacent to the anticodon region. The Q base, by the action of a transglycosylase, can be replaced with quanine; this reaction provides a method for detection of these unique tRNAs. Such Q base-containing tRNAs are present in a wide variety of tumors and, except for regenerating liver, are absent from normal tissues. Other tRNAs specific to tumors are under study.

With the rapid advancement of technology of cell culture, much new information is now available to assess the needs and requirements for growth of transformed cells and their relation to the endogenous synthesis of growth factors. Dr. Joseph DeLarco, National Cancer Institute, Bethesda, reported on the work of Dr. George Todaro's laboratory which has shown that the serum-free medium in which MSV-transformed cells are grown contains a factor that stimulates growth in cells arrested by serum depletion or confluence. This sarcoma growth factor (SGF) competes with the epidermal growth factor receptor in radioimmunoassay, and it is assumed that this is responsible for the apparent loss of EGF receptor in those cells. This substance, with a MW of 10,000, is one of several similar growth factors, separable by gel filtration.

Dr. Akira Ichihara, Tokushima University, found that in contrast with established liver cell lines, rat hepatocytes in primary culture, with the addition of insulin and dexamethasone, retained such adult liver functions as synthesis and secretion of liver proteins, glycogenolysis by glucagon, induction of tyrosine aminotransferase by dexamethasone, and of NADPH-generating dehydrogenases, DNA synthesis and polyamine formation by insulin. These cells did not proliferate, but over one week they gradually lost these functions, assumed an altered morphology, and enhanced activities of glycolytic enzymes.

Dr. Hiro Imura, Kyoto University School of Medicine, discussed another example of abnormal gene regulation, the ectopic production of polypeptide hormones by tumors of nonendocrine origin. An analysis of extracts of ACTH-producing tumors revealed the existence of "heavy" ACTH, together with smaller fragments with β-endorphin and β-LPH activity. In some instances ACTH activity was accompanied by calcitonin and chorionic gonadotropin. Production of multiple hormones by a single tumor was not uncommon, and experimental data suggest the formation of a large molecule precursor which splits into ACTH and smaller MW polypeptide hormones.

The presentations of participants who discussed host-tumor relationships brought additional support for the formation and release of bioactive substances as expressions of abnormal gene regulation in cancer. Dr. Olga Greengard, Mount Sinai

Medical Center, New York, reported that rats bearing a wide variety of neoplasms display striking alterations of liver enzyme activities, particularly in glucokinase and ornithine aminotransferase. These alterations are reversed with eradication of the tumor.

Dr. Kenneth Ibsen, University of California, Irvine, found similar effects on the isozymes of pyruvate kinase in livers of mice bearing Ehrlich ascites tumor, and partially purified what appears to be an active RNA-protein complex from these cells. A similar investigation, reported by Dr. Takehiko Tanaka, Osaka University Medical School, revealed a substance in Ehrlich ascites cells which lowers ornithine decarboxylase activity in liver, spleen, and kidney of treated mice. As little as 1 ϑg of a 70-fold purified preparation was active by i.p. injection in normal mice. It is a heat-labile, alkali-stable protein with MW > 300,000, and is inactivated by 10 mM dithiothreitol, 5 M urea, pronase, or glycosidase, but is stable to DNAse, RNAse, or neuraminidase.

Dr. Sidney Weinhouse, Fels Research Institute, Philadelphia, described work from his laboratory demonstrating a highly selective, reciprocal relationship between carbamyl phosphate synthetase (CPS-I) activity and urea synthesis in livers and tumors of rats bearing transplantable hepatomas. When these activities were high in the tumors, they were correspondingly low in the host liver. The existence of a humoral factor fostering homeostasis of urea production is suggested, although cross-circulation experiments in parabiotic rats failed to demonstrate effects of a tumor in one partner on the liver of the other normal partner.

Dr. Setsuro Fujii, Osaka University, following up previous reports of increased DNA synthesis in normal tissues of tumor bearing animals, found enhanced incorporation of thymidine kinase in liver and spleen of rats bearing the Yoshida or AH 130 sarcoma. This was accompanied by increased liver activities but decreased thymus activities of thymidine kinase, TMP kinase, and DNA polymerase. The responsible factor was partially purified. Dr. Fujii also described an inhibitor of ribonucleotide reductase in livers of normal rats which is altered in tumor bearers.

The proceedings of this conference attest to a growing recognition that a common feature underlying many of the phenotypic properties of cancer is an abnormality of gene regulation manifested by mis-programming of protein synthesis. This breach of the ordinarily regid control of gene activity in differentiated tissues accounts for the production of growth factors, oncofetal proteins, alterations of isoenzyme composition, and probably also the many varied effects of tumors upon host enzyme activities and metabolism. Consistent with this conception is the large and growing body of evidence that promoters function as inhibitors of differentiation in a variety of experimental systems.

Respectfully submitted,

Sidney Weinhouse
Professor of Biochemistry

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CANCER VIROLOGY
PROGRAM AREA REPORT

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Program Coordinators:
Dr. Yohei Ito
Dr. Robert McAllister

CANCER VIROLOGY PROGRAM AREA REPORT

October 1, 1977 to September 30, 1978

Administrative Report

MEETINGS, SEMINARS, AND CONFERENCES

The fourth Symposium to convene in this program area, "The Role of DNA Tumor Viruses in Cancer," was held in Honolulu, Hawaii, May 22 and 23, 1978. The participants were as follows:

For Japan	For the United States
Dr. Y. Ito	Dr. R. McAllister
Dr. K. Fujinaga	Dr. J. Frankel
Dr. H. Shimojo	Dr. J. Stevens
Dr. T. Osato	Dr. W. Henle
Dr. Y. Hinuma	Dr. W. Eckhart
Dr. S. Kato	Dr. M. Botchan
Dr. M. Ishibashi	Dr. J. Maizel
Dr. G. Kimura	Dr. G. Khoury
	Dr. M. Martin
	Dr. G. Theilan

The participants exchanged information about the mechanisms of oncogenesis by DNA tumor viruses at the molecular and cellular levels in the host. These basic findings were actively discussed in an effort to determine a possible etiologic role of DNA viruses in certain types of cancer in animals and in man.

EXCHANGE OF SCIENTISTS

Drs. John Moloney and Louis Sibal helped arrange a visit to the U.S. by Dr. Akira Seto of the University of Kyoto, September 1 through December 31, 1977. He visited Dr. R. Herberman (National Cancer Institute), Dr. P. Black (Harvard University), and Dr. G. Pearson (Mayo Clinic).

Dr. Yohei Ito invited Dr. Kenneth Takemoto to visit Japan (University of Tokyo; University of Kyoto; Tohoku University, Sendai; and Kumamoto University) October 3 through October 14, 1977, to give a series of lectures and workshops and to exchange information about human papovaviruses with the Japanese scientists.

Dr. Yoji Ikawa invited Dr. Richard Junghans of the California Institute of Technology to visit several institutions in Japan (Cancer Institute in Tokyo; University of Kyoto; Osaka University) from September 1 through September 23, 1977. Dr. Junghans demonstrated and discussed the heteroduplex mapping technique for nucleic acids.

Following the fourth Symposium in Honolulu in 1978, Dr. J. Frankel of the U.S. gave seminars at four Japanese academic institutes.

EXCHANGE OF MATERIALS

During 1977, plans were made for the Japanese to provide a number of cultured cell lines and for the United States to provide AMV reverse transcriptase and SPF laboratory animals.

Scientific Summary of Program Area

SUMMARY OF YEAR'S ACTIVITIES

Three sessions were held at the East-West Center in Honolulu, May 22 and 23, 1978, where investigators reported work on DNA tumor viruses. The abstracts of the meeting are included in the Five-Year Summary Report which follows this scientific summary.

SPECIFIC OBJECTIVES ACCOMPLISHED

The first four meetings of the two groups have stimulated good collaborative efforts among the Japanese and U.S. scientists. The meetings provided an excellent forum for exchanges of ideas concerning future collaborative cancer research efforts. Also, the personal contacts and mutual respect developed during the four meetings will lead to an enhancement of collaboration between scientists of both countries.

COOPERATIVE AND COLLABORATIVE ACTIVITIES RESULTING FROM PAST MEETINGS AND DISCUSSIONS

The exchange of scientists in both directions and the relaxed interactions at the four joint meetings are tangible evidence of the remarkable good will developed between our two countries.

Five-Year Summary Report, 1974 to 1978

ADMINISTRATIVE REPORT

Meetings, Seminars, and Conferences

The first Symposium on DNA and RNA tumor viruses, "Recent Advances in Tumor Virology," took place in Hilo, Hawaii, March 22 and 23, 1975. The participants were as follows:

For Japan	For the United States
Dr. Y. Ito	Dr. R. McAllister
Dr. H. Shimojo	Dr. J. Bishop
Dr. K. Fujinaga	Dr. M. Gardner
Dr. I. Osato	Dr. T. August
Dr. Y. Ikawa	Dr. F. Rapp
Dr. H. Yoshikura	Dr. W. Eckhart

Scientific sessions were devoted to papers and lively discussions of five classes of tumor viruses.

Presentations concerning DNA tumor viruses described the transforming activities and other gene functions of polyoma and SV-40 viruses. Studies of human adenovirus genomes in transformed hamster cells were reported. Cellular transformation by Epstein-Barr virus and by herpes simplex viruses were described as was the use of the Shope papilloma-carcinoma complex as a model for human cancer research.

Presentations concerning RNA tumor viruses included descriptions of the avian virus-host cell interactions. The natural history of the wild mouse type-C viruses and the host range and effects upon cellular differentiation by laboratory strains of mouse virus were reported. The characteristics of RD-114 virus in its extracellular type-C virus and intracellular DNA proviral forms were presented. The genetic expressions in mouse and human cells of type-C viral proteins and of infective viruses were also described.

Planning sessions were devoted to lengthy discussions addressing the general topic of how to effectively advance our knowledge of viruses in human carcinogenesis. Exchange of scientists, preprints, and materials were discussed, as were the topics and site for the next meeting of the Cancer Virus Groups. It was proposed that exchanges of preprints and reprints be on an individual scientist-to-scientist basis. Requests for materials should funnel through the Program Coordinators to their sources in each country.

The second Symposium, "Viral Oncogenesis Transmission, Persistence, and Expression of Viral Genome," was held in Kyoto, Japan, March 26 and 27, 1976. The participants were as follows:

For Japan	For the United States
Dr. M. Ishibashi	Dr. W. Eckhart
Dr. T. Miyamoto	Dr. J. Maizel
Dr. S. Kawai	Dr. J. Bishop
Dr. K. Toyoshima	Dr. P. Vogt
Dr. H. Yoshikura	Dr. M. Gardner
Dr. S. Kato	Dr. R. Gallo
Dr. T. Osato	Dr. R. McAllister
Dr. Y. Ito	

Three sessions were held at the Miyako Hotel on March 26 and 27, 1976. The investigators reported work on the entire spectrum of cancer virology, on culture of human cancer cells, and on possible interrelationships of chemical and viral carcinogenesis. The newest data were presented on the major groups of cancer viruses, namely, papovaviruses, adenoviruses, herpes viruses, and type-C RNA tumor viruses. These presentations ranged from basic molecular virology to implications of cancer in wild mice and humans, and the description of type-C viruses recovered from human acute myelocytic leukemia cells.

Drs. Hakura, Eckhart, and Kimura described the transforming and other gene functions of polyoma and SV-40 viruses as well as the relation between viral genes and host cells. Drs. Fujinaga, Shimojo, Ishibashi, and Maizel discussed the adenovirus proteins and viral genes in adenovirus-transformed cells. Drs. Miyamoto, Kawai, Bishop, Toyoshima, and Vogt discussed the genetics and physiology of avian type-C virus-cell interactions. Dr. Yoshikura discussed the role of chemical carcinogenesis in the induction of endogenous murine type-C virus. Dr. Gardner discussed the role of ecotropic and amphotropic type-C viruses in the pathogenesis of lymphoma and paralysis of wild mice in Los Angeles. Dr. Kato reported the establishment of Mareks lymphoma cell lines and the expression of herpes and type-C viruses in these lines. Dr. Osato discussed the possible influence of murine type-C virus upon the expression of Epstein-Barr virus in human cells. Dr. Gallo defined the relation between the woolly monkey and baboon type-C viruses and viruses from a patient with acute myelocytic leukemia. Dr. McAllister described the structure of RD-114 viral RNA and infectivity of viral DNAs from human and cat cells. And, Dr. Ito reported the properties of two lines of cells he established from human nasopharyngeal carcinomas.

The third Symposium, "Origin and Function of Oncogenic Sequences in RNA Tumor Viruses," was conducted in Pasadena, California, May 31 and June 1, 1977. The participants were as follows:

For Japan	**For the United States**
Dr. Y. Ito	Dr. R. McAllister
Dr. Y. Ikawa	Dr. N. Davidson
Dr. T. Yamamoto	Dr. M. Gardner
Dr. K. Toyoshima	Dr. D. Spector
Dr. T. Miyamoto	Dr. P. Besmer
Dr. M. Yoshida	Dr. P. Duesberg
Dr. T. Odaka	Dr. T. Shih
Dr. N. Tsuchida (observer)	Dr. J. Frankel

During these sessions, the participants reported on current and often unpublished studies about the origin, structure, and function of avian and mammalian RNA tumor viral genes.

The fourth Symposium, "Role of DNA Tumor Viruses in Cancer," was held May 22 and 23, 1978, in Honolulu, Hawaii. The participants were as follows:

For Japan	**For the United States**
Dr. Y. Ito	Dr. R. McAllister
Dr. K. Fujinaga	Dr. J. Frankel
Dr. H. Shimojo	Dr. J. Stevens
Dr. T. Osato	Dr. W. Henle
Dr. Y. Hinuma	Dr. W. Eckhart
Dr. S. Kato	Dr. M. Botchan
Dr. M. Ishibashi	Dr. J. Maizel
Dr. G. Kimura	Dr. G. Khoury
	Dr. M. Martin
	Dr. G. Theilan

The participants exchanged information about the mechanisms of oncogenesis by DNA tumor viruses at the molecular and cellular levels in the host. These basic findings were actively discussed in an effort to determine a possible etiologic role of DNA viruses in certain types of cancer in animals and in man.

Exchange of Scientists

During the Spring and Summer of 1975, Dr. Fumio Mizuno worked at the National Cancer Institute, Bethesda, Maryland, and the Presbyterian-Rush Medical School, Chicago, Illinois.

Before and after the second Symposium in Kyoto in 1976, seven American scientists visited nine institutions in Japan to exchange information, to give thirteen seminars, and to make plans for collaborative projects and for possible exchange visits. These visits are outlined below:

Dr. Walter Eckhart. Department of Tumor Virus Research, Institute of Medical Sciences, University of Tokyo; Department of Microbiology, University of Kyoto; Department of Virology and Bacteriology, Tottori University School of Medicine; and Department of Tumor Viruses, Research Institute for Microbial Diseases, Osaka University.

Dr. Peter Vogt. Department of Tumor Viruses, Research Institute for Microbial Diseases, Osaka University; Department of Biochemistry, Cancer Institute, Okayama University School of Medicine; Department of Microbiology, Kumamoto University School of Medicine; and Department of Tumor Virus Research, Institute of Medical Sciences, University of Tokyo.

Dr. Robert Gallo. Department of Microbiology. Kyoto University.

Dr. J. Michael Bishop. Department of Microbiology, Kyoto University; Department of Tumor Viruses, Institute for Microbial Diseases, Osaka University; and Institute for Cancer Research, University of Tokyo.

Drs. Murray Gardner and Robert McAllister. Radiation Effects Research Foundation, Hiroshima.

Dr. Jacob Maizel. Department of Microbiology, Osaka University.

A number of collaborative endeavors are underway. Dr. Hakura (from Dr. Toyoshima's laboratory) and Dr. Kimura (of Tottori University) will conduct experiments with Dr. Eckhart. Drs. Fumio Mizuno and Masahide Ishibashi conducted experiments in the United States. Dr. Oda's group discussed their plans for avian tumor virus research with Dr. Vogt. Other scientists from both sides are considering collaborative ventures and possible exchange visits.

Before the third Symposium in Pasadena in 1977, Drs. Y. Ikawa, M. Yoshida, and K. Toyoshima attended and presented papers at the Cold Spring Harbor meeting "RNA Tumor Viruses." After the Pasadena meeting, some Japanese scientists visited the University of Southern California, the California Institute of Technology, and the National Cancer Institute to exchange information, to give seminars, and to make plans for collaborative projects and possible exchange visits.

Drs. John Moloney and Louis Sibal helped arrange a visit to the U.S. by Dr. Akira Seto of the University of Kyoto, September 1 through December 31, 1977. He visited Dr. R. Herberman (National Cancer Institute), Dr. P. Black (Harvard University), and Dr. G. Pearson (Mayo Clinic).

Dr. Yohei Ito invited Dr. Kenneth Takemoto to visit Japan (University of Tokyo; University of Kyoto; Tohoku University, Sendai; and Kumamoto University) October 3 through October 14, 1977, to give a series of lectures and workshops and to exchange information about human papovaviruses with the Japanese scientists.

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Dr. Junghans demonstrated and discussed the heteroduplex mapping technique for nucleic acid.

Following the fourth Symposium in Honolulu in 1978, Dr. J. Frankel, of the United States, gave seminars at four Japanese academic institutes.

Exchange of Resources and Materials

Over the past five years, the following materials were exchanged between scientists from Japan and the U.S.:

> In 1975, a set of materials requested by Dr. Yoji Ikawa was sent to him by the office of Program Resources and Logistics, National Cancer Institute. During 1976, 500 ml of erythropoietin from a pool which is ARG-567-Ta LSL (this pool had a specific activity of 52.7 units per mg.) was sent by Dr. Peter Dukes to Dr. Ikawa for his research work on induction of differentiation of Friend virus-induced leukemia cells.
>
> Dr. Ikawa also received from Dr. Jack Gruber avian myeloblastosis virions and antisera to type-C viruses. These were used by him and by Drs. T. Osato, K. Fujinaga, and others for studies of viral etiology of human cancer.
>
> Dr. G. Kimura gave his 3Y-1 rat cell line to Dr. W. Eckhart for studies of virus-induced transformation.
>
> During 1977, plans were made for the Japanese to provide a number of cultured cell lines and the U.S. to provide AMV reverse transcriptase and SPF laboratory animals.

SCIENTIFIC SUMMARY OF PROGRAM AREA

Extent and Manner in Which Cooperative Activities Have Provided Impact or Influence on the Two Countries

During our mutual interaction over the past five years, scientists from Japan and the U.S. have developed a mutual respect and quiet confidence in each other that will lead to ever-widening areas of scientific cooperation, in the mutual exchange of scientists (both senior and junior), preprints, and materials.

Subsequent developments depend upon maintaining and widening the respect and cooperation that have been established during our five year collaboration. In the future, we must continue our present annual interaction and, specifically, include young scientists from both countries who will carry these achievements of mutual respect into the future.

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CANCER IMMUNOLOGY PROGRAM AREA REPORT

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Annual Meeting and Symposium: Immunology and Cancer
(Maui, Hawaii)

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Workshop on Immunological Xenogenization of Tumor Cells
(Sapporo, Japan)

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Program Coordinators:
Dr. William Terry
Dr. Yuichi Yamamura

CANCER IMMUNOLOGY PROGRAM AREA REPORT

October 1, 1977 to September 30, 1978

Administrative Report

The joint efforts of American and Japanese scientists in the Cancer Immunology Program Area can be divided into three groups: Meetings, Seminars, and Conferences; the Exchange of Scientists; and the Exchange of Resources and Materials.

MEETINGS, SEMINARS, AND CONFERENCES

The Annual Meeting of this Program Area and a Symposium entitled "Immunology and Cancer" were held in Maui, Hawaii, on September 25 to 27, 1978. The agenda and lists of participants follow this Program Area Report.

A workshop on Immunological Xenogenization of Tumor Cells was held in Sapporo, Japan. The formal workshop was held on June 6 to 8, 1978, and Special Lectures on Cancer Research were presented on June 5 and June 9. This workshop, organized by Dr. Hiroshi Kobayashi, was partially supported with funds from the U.S. and was attended by 7 Americans, 35 Japanese, and 6 scientists from other countries. Although this workshop was not directly under the auspices of the U.S.-Japan Cooperative Cancer Research Program, the American participation and support was facilitated by the U.S.-Japan Program. The agenda and list of participants follow this Program Area Report.

EXCHANGE OF SCIENTISTS

The name of each visiting scientist is followed by his address, the date of his visits, the names and addresses of all host scientists, and a brief description of techniques studied.

1. *Takashi Mori*, M.D.
Chief of the Second Department of Surgery
National Kinki Central Hospital for
Chest Diseases
1180 Nagazone-Cho
Sakai City, Osaka 591, Japan

Dates: September 16-December 10, 1977

Hosts: Dr. Hiroshi Takita
Roswell Park Memorial Institute
Buffalo, New York 14203, U.S.A.

Dr. William Terry
National Cancer Institute
Bethesda, Maryland 20014, U.S.A.

Dr. Herbert Oettgen
Memorial Sloan-Kettering
Cancer Center
1275 York Avenue
New York, New York 10021, U.S.A.

Dr. Martin McKneally
Albany Medical College
Albany, New York 12208, U.S.A.

Dr. Michael Mastrangelo
American Oncologic Hospital
Fox Chase Cancer Center
Philadelphia, Pennsylvania 19111,
U.S.A.

Dr. Evan Hersh
M.D. Anderson Hospital and
Tumor Institute
University of Texas
Houston, Texas 77025, U.S.A.

Dr. E. Carmack Holmes
University of California at Los Angeles
Los Angeles, California 90024,
U.S.A.

Dr. Mori visited various laboratories that were working in the field of immunotherapy of cancer and observed clinical techniques used in the administration of immunotherapeutic drugs in the treatment of cancer, particularly cancer of the lung.

2. *Dr. Kosei Yasumoto*
Department of Chest Surgery
Kyushu Cancer Institute
Minamiku Fukuoka
595 Notame 815, Japan

Dates: March 1-31, 1978

Hosts: Dr. E. Carmack Holmes
University of California at Los Angeles
Los Angeles, California 90024,
U.S.A.

Dr. Hiroshi Takita
Roswell Park Memorial Institute
Buffalo, New York 14263, U.S.A.

Dr. Martin McKneally
Albany Medical College
Albany, New York 12208, U.S.A.

Dr. James Holland
Mount Sinai School of Medicine
New York, New York 10029, U.S.A.

Dr. William Terry
National Cancer Institute
Bethesda, Maryland 20014, U.S.A.

Dr. Yasumoto visited various laboratories that are working in the field of immunology and immunotherapy of cancer and observed clinical techniques used in the administration of immunotherapeutic drugs in the treatment of cancer, particularly lung cancer.

3. *Dr. Kazuhisa Sugimura*
Postgraduate Student
The Third Department of Internal Medicine
Osaka University Hospital
Fukushima-ku
Osaka, Japan

Dates: April 1-December 31, 1978

Hosts: Dr. Harvey Cantor
Sidney Farber Cancer Center
Harvard Medical School
Boston, Massachusetts 02115, U.S.A.

Dr. Sugimura visited this laboratory and studied lymphocyte antigens.

4. *Dr. H. Terry Wepsic*
Staff Pathologist, VA Hospital
Assistant Professor in Residence
Department of Pathology
University of California
San Diego, California 92161, U.S.A.

Dates: July 1, 1978-June 30, 1979

Host: Dr. Hidematsu Hirai
University of Hokkaido School of
Medicine
Sapporo, Japan

Dr. Wepsic studied tumor antigens of rat yolk-sac tumors. This one-year sabbatical was arranged under the auspices of the U.S.-Japan Cooperative Cancer Research Program. Its expenses, however, were not funded through this Program.

5. *Dr. Hiromi Fujiwara*
Institute for Cancer Research
Osaka University Medical School
Osaka, Japan

Dates: June 1, 1978-May 30, 1979

Host: Dr. William Terry
National Cancer Institute
Bethesda, Maryland 20014, U.S.A.

Dr. Fujiwara was a Visiting Fellow in the Fogarty International Program of the National Institutes of Health, Bethesda, Maryland. Although Dr. Fujiwara was not directly supported by the U.S.-Japan Program, his visit in the Immunology Branch of the National Cancer Institute was very much facilitated by the interactions between the late Dr. Masayasu Kitagawa and Dr. Terry that took place during the activities of the U.S.-Japan Cooperative Cancer Research Program.

EXCHANGE OF RESOURCES AND MATERIALS

Dr. Ichiro Azuma and Dr. Yuichi Yamamura sent 2 grams of the cell-wall skeletons of BCG and *Nocardia rubra*, of which 200 mg of each were distributed to Dr. Ronald Herberman of the National Cancer Institute, Bethesda, Maryland.

Scientific Summary of Program Area

The major accomplishments in this program area have been a consequence of the exchanges of information, reagents, and personnel.

INFORMATION EXCHANGE

Research Information. Both countries are developing approaches to clinical immunotherapy. This information would usually not be in the literature for several years and would usually be presented at meetings not attended by scientists of both countries. The annual meetings and symposia have provided a forum for exchange of up-to-date information and this information has modified activities. For example, reports on the use of intrapleural BCG cell-wall skeleton in Japan have stimulated interested scientists in the United States to clinical applications of this material. Similarly, reports of the use of intrapleural BCG in the treatment of stage I lung cancer in the U.S. have alerted Japanese clinicians to this clinical application. It is anticipated that trials presently under way in each country will lead to an opportunity to compare results within several years.

Application Information. In both countries, clinical activities, either diagnostic or therapeutic, occasionally obtain unusual publicity and stimulate great public interest within the other country. The U.S.-Japan Cooperative Cancer Research Program has served as a clearinghouse for evaluation of these activities. This has been important in permitting rapid and accurate responses to the public inquiries about the real value of alleged diagnostic tests or treatments in a manner that would not be possible without this Program.

EXCHANGE OF RESOURCES AND MATERIALS

Exchange of reagents has involved derivatives of BCG organisms prepared in Japan and sent to the U.S. where studies of the activities of these materials in other immunotherapeutic models have been carried out. American scientists have supplied Japanese scientists with some inbred strains of animals not generally available.

EXCHANGE OF SCIENTISTS

The exchange of personnel has been facilitated by the Program. Contacts made at the annual meetings have led to a better understanding of the specific types of investigations being carried out in each laboratory, thus leading to a better placement of junior scientists in laboratories most appropriate to their research interests.

FUTURE OBJECTIVES

Experience to date makes it clear that a broadening of the Program into other areas of the biology of cancer—cell biology, molecular biology, and immunobiology—will be desirable. Many of the limitations in present approaches to immunotherapy and immunodiagnosis are due to our inadequate knowledge of the basic biology of the systems with which we deal. A collaborative program to widen knowledge in these areas can further benefit the scientists of both Japan and the United States.

CONFERENCE REPORTS

SYMPOSIUM: IMMUNOLOGY AND CANCER

Maui, Hawaii

September 25 to 27, 1978

AGENDA

Monday, September 25

TUMOR ASSOCIATED IMMUNITY

8:45 a.m.	Introductory Comments	**Yuichi Yamamura** **William Terry**
9:05 a.m.	*In Vitro* Introduction of Tumor Specific Immunity	**Noel Warner**
9:40 a.m.	The Cellular Basis of Cytotoxic T Cell Responses to Tumors	**Chris Henney**
10:15 a.m.	Characterization of ADCC in Man	**Albert LoBuglio**
10:50 a.m.	COFFEE BREAK	
11:05 a.m.	Cell Mediated Cytotoxic Responses to Human Melanoma Target Cells	**Michael Bean**
11:40 a.m.	Serological Typing of Cell Surface Antigens of Human Malignant Melanoma	**Toshitada Takahashi**
12:15 p.m.	Serological Typing of Cell Surface Antigens of Human Renal Cancer and Astrocytoma	**Hiroshi Shiku**

CHARACTERIZATION OF IMMUNE CELLS

7:30 p.m.	Expression of I Region Gene Products on Accessory Cell Populations	**Richard Hodes**
8:05 p.m.	Distribution of T and B Cells in Cancer Tissues	**Kokichi Kikuchi**
8:40 p.m.	Characterization of Murine T and B Cell Lymphomas Through Quantitative Analysis of Cell Surface Marker Expression	**Noel Warner**

Tuesday, September 26

SUPPRESSION OF IMMUNE RESPONSES

8:30 a.m.	Selective Stimulation and Inactivation of Suppressor T Cells in Tumor Immunology	**Tomio Tada**
9:05 a.m.	Suppressor T Cells and Suppressor Macrophages: Their Induction and a Comparison of their Mechanism of Action	**Chris Henney**
9:40 a.m.	Suppressor Cells in Ultraviolet Carcinogenesis	**Richard Thorn**
10:15 a.m.	COFFEE BREAK	
10:30 a.m.	Restricted Suppressor T Cell Activity in the Blood of a Patient with Recurrent Bladder Carcinoma	**Michael Bean**
11:05 a.m.	Suppressor Cells in Tumor Bearing Individuals	**Ronald Herberman**

MACROPHAGES

11:40 a.m.	Studies on the Role of Oxidative Metabolism in the Tumor Cell Cytotoxicity of Activated Macrophages	**Carl Nathan**
12:15 p.m.	Activation of Tumoricidal Macrophages with Lymphokines	**Toru Tokunaga**

NATURAL KILLER CELLS

7:30 p.m.	Natural Killer Cells: Their Mechanism of Action and Possible Significance in Neoplasia	**Chris Henney**
8:05 p.m.	Natural Cell Mediated Cytotoxicity Against Tumors: Nature of Effector Cells and Factors Affecting Activity	**Ronald Herberman**
8:40 p.m.	Approaches to the Identification of the Natural Killer Cell and its Target Cell Specificity	**Noel Warner**
9:15 p.m.	Active Immunization With Xenogenized Tumor Cells	**Hiroshi Kobayashi**

Wednesday, September 27

PRECLINICAL IMMUNOTHERAPY

8:30 a.m.	Immunotherapy of Cancer With *Nocardia Rubra* Cell Wall Skeleton	**Yuichi Yamamura**
9:05 a.m.	Synthetic Immunotherapeutic Agents	**Ichiro Azuma**

Wednesday, September 27 (continued)

PRECLINICAL IMMUNOTHERAPY

9:40 a.m.	Specific Immunotherapy of Established Visceral Micrometastases by BCG Tumor Cell	**Michael Hanna**
10:15 a.m.	COFFEE BREAK	
10:30 a.m.	Experimental Immunotherapy of Cancer With Cell-Wall Skeletons of BCG and *Nocardia Rubra*	**Takeshi Ogura**
11:05 a.m.	Correlation Between Antigenicity of Cancer Cells and Therapeutic Effect of Immunopotentiators	**Yoshiyuki Hashimoto**
11:40 a.m.	Treatment of Established Micrometastases by Injection of Tumoricidal Macrophages	

CLINICAL IMMUNOTHERAPY

1:30 p.m.	The Immunotherapy of Acute Myelogenous Leukemia Using Cell-Wall Skeletons of BCG and *Nocardia Rubra*	**Kazuhisa Yamada**
2:05 p.m.	Preoperative intralesional BCG Immunotherapy of Lung Cancer	**E. Carmack Holmes**
2:40 p.m.	Immunotherapy of Lung Cancer With the Cell-Wall Skeletons of BCG and *Nocardia Rubra*	**Kenji Sawamura**

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WORKSHOP ON
IMMUNOLOGICAL XENOGENIZATION OF TUMOR CELLS

June 6-8, 1978

Park Hotel
Sapporo, Japan

AGENDA

Tuesday, June 6

9:00 a.m.	Opening Remarks	**H. Kobayashi**
9:05 a.m.	Opening Remarks	**C. W. Boone**

Session 1A: Xenogenization with Virus

Co-chairmen: **G. J. Svet-Moldavsky** and **J. Lindenmann**

9:15 a.m.	Xenogenization by Viruses: How Could it Work?	**J. Lindenmann**
9:55 a.m.	Augmented TATA Immunogenecity of Membranous and Soluble Extracts from Tumor Cells Infected with Surface Budding Virus	**C. W. Boone**
10:35 a.m.	COFFEE BREAK	
10:50 a.m.	Artificial Heterogenization (Xenogenization) of Tumors	**G. J. Svet-Moldavsky**
11:30 a.m.	Immunogenicity of Virus-Infected Xenogenized Tumor Cells	**H. Kobayashi** and **F. Sendo**
12:10 p.m.	Increased Immunogenicity of Rat Tumors After Infection With Endogenous Murine C-type Virus	**N. Kuzumaki** and **G. Klein**

Session 1B: Xenogenization with Virus

Co-chairmen: **C. W. Boone** and **H. Uetake**

2:00 p.m.	Stabilized Expression of Tumor-Associated Antigen in Xenogenized Tumor Cells to Complement Dependent Cytotoxicity	**E. Gotohda** and **T. Kodama**

Tuesday, June 6 (continued)

2:40 p.m.	The Role of Virus-Associated Antigen on Xenogenized Tumor Cell Surface in Production of Antibody Against Tumor-Associated Antigen	**T. Moriuchi**
3:10 p.m.	Increased Immunosensitivity of Xenogenized Tumor Cells to Lymphocyte Cytotoxicity	**M. Hosokawa**
3:50 p.m.	COFFEE BREAK	
4:10 p.m.	Induction of Immune resistance by HVJ-infected L1210 Cells	**K. Yamada**
4:50 p.m.	Decreased Transplantability of Cultured Tumor Cells Persistently Infected with Nononcogenic Viruses	**M. Hatano**
5:20 p.m.	Breakdown of MuL V-Induced Tolerance and Subsequent Regression of Xenogenized Tumors	**N. Takeichi**

Wednesday, June 7

Session 2A: Xenogenization with Chemicals and Enzymes

Co-chairmen: **G. M. Shearer** and **Y. Hashimoto**

9:00 a.m.	Enhanced Immunogenecity of Concanavalin A Coated Tumor Cells	**W. J. Martin**
9:40 a.m.	Induction of Immune Resistance to L1210 Murine Leukemia by Lectin-Bound Tumor Vaccine	**T. Kataoka**
10:00 a.m.	Induction of Immune Resistance Against Tumor in a Low Responsive Tumor-Host Combination by Immunization With Chemically Modified Tumor Cells in the Presence of the Chemicals-Reactive Helper T Cells	**T. Hamaoka**
10:40 a.m.	COFFEE BREAK	
10:55 a.m.	Induction of Immunity with Fluorescence-Haptenized Tumor Cells and Liposomes	**Y. Hashimoto**
11:20 a.m.	Immunoprophylaxis and Therapy With Lipid Conjugated Lymphoma Cells	**M. D. Prager**
12:00 noon	Alteration of Immunosensitivity in Nitrogen Mustard-Resistant Yoshida Sarcoma Cells	**S. Tsukagoshi**

Wednesday, June 7 (continued)

Session 2B: Recognition of Cell Surface Antigens Undergoing Xenogenization

Co-chairmen: **N. A. Mitchison** and **T. Tada**

2:00 p.m.	Non-Enveloped Virus-Induced Specific Cell Surface Antigen(s) and Its Role in Cell-Mediated Immunity	**H. Uetake, T. Inada,** and **S. Hasegawa**
2:30 p.m.	Development and Alternate Changes of Surface Antigen in Adenovirus Type 12-Infected and Transformed Cells	**C. Hamada**
2:50 p.m.	MHC-Restriction of T-Cell Recognition	**R. M. Zinkernagel**
3:30 p.m.	COFFEE BREAK	
3:45 p.m.	Associate Recognition in the Response to Allo-Antigens (and Xenogenization of Allo-Antigens)	**N. A. Mitchison**
4:25 p.m.	Differential Recognition of Tumor Antigens by Cytotoxic and Suppressor T Cells	**T. Tada**
5:00 p.m.	Recognition of RSV-Induced Tumor Cells in Syngeneic Mice and Semi-Syngeneic Reciprocal Hybrid Mice	**Takato Yoshida**
5:20 p.m.	Genetic Regulation of Immune Responses to TNP-Modified Cells	**G. M. Shearer**

Thursday, June 8

Session 3A: Xenogenization by Cell-Hybridization

Co-chairmen: **A. J. S. Davies** and **T. Tachibana**

9:00 a.m.	Antigenic Expression on Somatic Cell Hybrids in Relation to the Potential Use of Hybridization for Tumor Xenogenization	**G. Klein**
9:40 a.m.	Antigenic Expression on Mouse Hybrid Cells	**T. Tachibana**
10:20 a.m.	COFFEE BREAK	
10:35 a.m.	Immune Response to Hybrid Cells in Normal and Tumor-Bearing Mice	**T. Dei**
11:15 a.m.	Liposomal Fusion as a Means of Introducing Surface Antigens Into Living Cell Membranes	**A. J. S. Davies**
11:55 a.m.	Open Discussion	

Thursday, June 8 (continued)

Session 3B: Application of Xenogenization to Human Cancer
Co-chairmen: **G. Klein** and **T. Aoki**

2:00 p.m.	Melanoma Skin Test Antigens of Improved Sensitivity Prepared from Vesicular Stomatitis Virus-Infected Tumor Cells	**C. W. Boone**
2:30 p.m.	Vaccinia Virus Augmented Tumor Vaccine as a New Form of Immunotherapy.	**M. K. Wallack**
3:00 p.m.	COFFEE BREAK	
3:15 p.m.	Attempts at Virus-Associated Immunotherapy in Human Cancer	**J. Lindenmann**
3:45 p.m.	Oncotropic Viruses and Problems in Virotherapy	**A. J. Muceniece**

SPECIAL LECTURES

Park Hotel
Sapporo, Japan

Monday, June 5, 1978

Epstein-Barr Virus, Infectious Mononucleosis, Burkitt's Lymphoma and Nasopharyngeal Carcinoma
Chairman: **Toyoro Osata** Speaker: **George Klein**

Thursday, June 8, 1978

Immunotherapy of Tumor with BCG and Nocardia Cell Wall Skeleton
Chairman: **Hiroshi Kobayashi** Speaker: **Yuichi Yamamura**

LECTURES ON CANCER RESEARCH

Centennial Hall
Hokkaido University (Hokudai)
Sapporo, Japan

Friday, June 9, 1978

10:00 a.m. Regulation of the Immune Response by Ia-Antigen Complexes

Chairman: **M. Aizawa**
Speaker: **N. A. Mitchison** (UK)

10:40 a.m. Derepressed Histocompatibility Alloantigen on Transplacentally Induced Murine Lung Tumors

Chairman: **F. Sendo**
Speaker: **W. J. Martin** (USA)

11:20 a.m. Long-Term Studies of the Lymphoid System of the Mouse

Chairman: **K. Kikuchi**
Speaker: **A. J. S. Davies** (UK)

1:30 p.m. Immune Response, Protection and Autoimmunity Following Immunization of Mice With Modified Syngeneic Tumor Cells

Chairman: **H. Hosokawa**
Speaker: **M. D. Prager** (USA)

2:10 p.m. Paradoxical Age-Dependent Features of Growth of Transplanted Fetal Tissues and Tumors

Chairman: **H. Kobayashi**
Speaker: **G. Svet-Modavsky** (USSR)

2:50 p.m. Spontaneous Neoplastic Transformation *in vitro* and its Relationship to Plastic Film Tumorigenesis

Chairman: **M. Sasaki**
Speaker: **C. W. Boone** (USA)

3:30 p.m. Oncolytic Enteroviruses in Experiment and Clinics

Chairman: **T. Kodama**
Speaker: **A. J. Muceniece** (USSR)

4:10 p.m. Adjuvant Therapy of Carcinoma of the Colon and Rectum with Vaccinia Oncolysates

Chairman: **T. Tanabe**
Speaker: **M. K. Wallack** (USA)

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CANCER CHEMOTHERAPY PROGRAM AREA REPORT

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CONFERENCE REPORT

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Program Coordinators:
Dr. Yoshio Sakurai
Dr. Stephen K. Carter

CANCER CHEMOTHERAPY PROGRAM AREA REPORT

September 1977 to October 1978

Administrative Report

Progress begun in earlier years in this program area continued during this fifth year of the U.S.-Japan Cooperative Cancer Research Program. The chemotherapy aspect has worked on three fronts: (1) the exchange of information, (2) the exchange of drugs, and (3) collaborative studies.

MEETINGS, SEMINARS, AND CONFERENCES

Information exchange took place on a variety of levels and symposia continue to play an important role. In November 1977, the Princess Takamatsu Symposium was held on the subject of cancer chemotherapy. Dr. Stephen K. Carter and Dr. Abraham Goldin were the foreign co-organizers of the Symposium. American participants included Dr. Franco Muggia, Dr. Phillip Schein, Dr. Robert Livingston, Dr. Joseph Bertino, Dr. Emil Freireich, Dr. Michael Friedman and Dr. Norman Jaffe. This meeting, while not an official part of the U.S.-Japan Cooperative Cancer Research Program, was another important opportunity for U.S. and Japanese investigators to meet and discuss their many areas of mutual interest. During the same period, small meetings were held concerning PEP-bleomycin, bestatin, and the U.S.-Japan Gastric Cancer Study.

In June 1978, the program review symposium was held on the methodology of Phase I and Phase II studies with emphasis on analogues. Drug classes of emphasis were the anthracycline antitumor antibiotics, bleomycins, nitrosoureas, and fluorinated pyrimidines. The agenda and a list of the participants at this symposium follow this Program Area Report. The papers from this meeting will be published in the new journal, *Cancer Chemotherapy and Pharmacology*.

The previous year's Symposium on Antitumor Antibiotics, which was held in San Francisco on May 25 and 26, 1977, has now been published as Volume 63 of *Recent Results in Cancer Research*, published by Springer-Verlag, 1978, Berlin, Heidelberg and New York.

EXCHANGE OF MATERIALS

Several Japanese drugs continued in clinical study in the United States. Neocarzinostatin is now in Phase II trials in a range of U.S. institutions. At the Sidney Farber Cancer Institute activity has been observed in hepatomas which has led to several trials in this tumor. Drugs under preclinical study at the NCI include aclacinomycin-A, PEP-bleomycin, and bestatin. Aclacinomycin-A has also been studied preclinically by the Multidisciplinary Drug Research Group of the Northern California Cancer Program, and the Northern California Oncology Group (NCOG) is awaiting a decision by the NCI concerning filing an IND for the drug with the Food and Drug Administration (FDA). The NCOG is interested in performing Phase I study on the drug.

COLLABORATIVE STUDIES

In the past year a joint collaborative chemotherapy study of advanced gastric cancer was begun between the NCOG and selected Japanese investigators. This study involved a common arm between the U.S. and Japanese investigators which is adriamycin plus 5-FU. This is compared in the NCOG to an American arm of BCNU, adriamycin, and ftorafur and in Japan to an arm of mitomycin-C, adriamycin, and ftorafur. Randomization is performed through the NCOG statistical office which will also be doing the statistical analysis of the data. The study has nearly 50 cases entered and is a logistical success. The fact sheet and schema of the protocol are presented below.

UNITED STATES-JAPAN JOINT PROTOCOL FOR ADVANCED GASTRIC CANCER

PROTOCOL NUMBER 3S62

NORTHERN CALIFORNIA ONCOLOGY GROUP
1801 Page Mill Road
Building B, Suite 200
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SITE: stomach
HISTOLOGY: adenocarcinoma
STAGE: disseminated
VARIABLE: common arm: Adriamycin + 5-FU
U.S. arm: BCNU + Adriamycin + Ftorafur
Japan Arm: Mitomycin C + Adriamycin + Ftorafur
MODALITIES: chemotherapy

TITLE: A Phase III Study Comparing Adriamycin + 5-FU versus BCNU + Adriamycin + Ftorafur versus Mitomycin C + Adriamycin + Ftorafur for Patients with Disseminated Gastric Cancer

	UNITED STATES	JAPAN
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CO-STUDY CHAIRMAN:	Karen Fu, M.D. University of California	Yoshiyuki Koyama, M.D. National Medical Center Hospital
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STUDY SECRETARY:	Michael Friedman, M.D. University of California	Makoto Ogawa, M.D. Aichi Cancer Center Hospital
DISEASE COMMITTEE CHAIRMAN:	Michael Friedman, M.D. University of California	Kiyoji Kimura, M.D. National Cancer Center Hospital
PARTICIPANTS:	Entire Group	
DATE ACTIVATED:	5 December 1977	

Five-Year Summary Report

The past five years have brought great benefits to both countries. The interaction between U.S. and Japanese scientists interested in cancer chemotherapy has moved through the stages of communication, cooperation, and collaboration. The communication has involved exchange of information concerning methodology of anticancer drug development, methodology of clinical evaluation of new drugs, and new drugs under clinical investigation. This has been accomplished through joint symposia, exchange of scientists, and an extensive exchange of written material. As a result of these communications, improvements in drug development techniques have occurred in both countries. Model systems from both countries have become part of the screening and analogue delineation approaches in both countries. The Japanese Institute for Cancer Research's Cancer Chemotherapy Center has set up a screening program for new drugs which utilizes the screening protocols of the National Cancer Institute (NCI) and which feeds data into their system. A leading source of new fermentation structures for the NCI natural product program has come from the Japanese Institute for Microbial Research under the brilliant leadership of Professor Hamao Umezawa. The close working relationship that has developed between Professor Umezawa and his institute and the NCI drug development program has been one of the major benefits of the U.S.-Japan Cooperative Cancer Research Program to the United States. Among the new drugs which have entered into the NCI drug development program from Professor Umezawa are the following: macromomycin, diketocariolan, bestatin, PEP-bleomycin, and aclacinomycin-A.

Japanese drugs which have undergone clinical trial in the U.S. in the last five years include: chromomycin A_3, cyclocytidine, yoshi-864, and neocarzinostatin.

One of the most important areas of cooperation and collaboration between the two countries has been in the area of analogue drug development. The thrust of analogue development is to take an active structure and attempt to improve its therapeutic index by increasing the efficacy and/or diminishing the toxicity. This has been one of the strongest areas of interaction in the U.S.-Japan Agreement. Four areas have been highlighted for work and these exemplify the truly international flavor of the agreement: (1) the nitrosoureas—compounds developed in the United States by the NCI drug development program; (2) bleomycins—antitumor antibiotics discovered by Umezawa in Japan; (3) anthracyclines—originally developed in Italy with major clinical evaluation in the U.S.; and (4) ftorafur and the fluoridated pyrimidines—an approach originally developed in the U.S.S.R. with major clinical testing and secondary development in Japan.

Work in the nitrosoureas has centered around diminishing the marrow toxicity of this class of drugs by the inclusion of a sugar moiety in the structure. Two closely related compounds have been independently synthesized in the two countries. They are chlorozotocin in the United States and GANU in Japan. As part of the exchange, these two drugs have been compared in the laboratories of both countries. Testing has concentrated on the relative alkylating and carbamoylating activities of both drugs in an attempt to understand the mechanisms of antitumor effect and toxicity with hope of being able to separate them. While the two drugs are very closely related structurally, they have different ratios of the two effects. The two drugs are either in the clinic or will be quite soon. When the clinical results are correlated with the laboratory data the stage should be set for a new understanding which could lead to more rational continued analogue development. This scientific cooperation and collaboration has greatly enriched the programs in both countries.

Bleomycin is one of the most important anticancer drugs of the 1970s. The drug has activity against a range of squamous cell cancers as well as lymphomas and testicular cancer. It is remarkable for its lack of bone marrow toxicity and for its propensity to cause pulmonary fibrosis. Originally developed in Japan it has been extensively tested in the United States. Throughout the five years of the Agreement, several symposia have involved an exchange of the clinical results from both countries. These exchanges have enriched the clinical value of this drug in the U.S. and Japan. Bleomycin is now an integral part of curative treatments for testicular cancer and the malignant lymphomas. Dr. Umezawa and his co-workers have synthesized more than 200 analogues of bleomycin in hopes of improving the therapeutic index. The strategy for the experimental testing of these analogues has been a major point of discussion in past meetings.

Adriamycin is an anthracycline antitumor antibiotic developed in Italy by the Farmitalia company. Its major clinical testing was performed in the United States. It has the broadest spectrum of any cancer drug that has ever been developed. Its use is limited by a propensity to cause cardiomyopathy.

Analogue development to diminish the cardiac toxicity has been extensive. New compounds have come from Japan (aclacinomycin-A), the U.S. (AD-32), the U.S.S.R. (carminomycin), and France (rubidazone). The structure for clinical and experimental testing has been an important aspect of several symposia sponsored by the U.S.-Japan Agreement. It is expected that clinical testing of aclacinomycin will soon begin in the United States.

Ftorafur is a fluorinated pyrimidine analogue of 5-fluorouracil originally synthesized in the U.S.S.R. Extensive clinical testing took place in Japan where the drug is commercially available. Investigational clinical study has also taken place in the U.S. and still continues. Several new analogues have been synthesized in Japan (FD-1, HCFU) and have been discussed at recent symposia.

Another important area of communication and collaboration under the Agreement has been the treatment of stomach cancer. Gastric cancer is the leading cause of cancer death in Japan and, while diminishing in incidence, is still the seventh leading cause of cancer death in the United States. In the past years there has been both exchange of scientists and symposia emphasizing this area. A group of speakers from the U.S. Gastrointestinal Tumor Study Group visited Japan and participated in a symposium on the treatment of gastric cancer. On several occasions, Japanese scientists have come to the U.S. and participated in the meetings of the Gastrointestinal Tumor Study Group. Until recently clinical research into gastric cancer in the U.S. had been a neglected area. The important upsurge of interest in this important tumor in the U.S. has been helped by the extensive knowledge about this tumor area developed in Japan. This has all culminated in a collaborative protocol being initiated by the Northern California Oncology Group of the Northern California Cancer Program and several Japanese centers under the coordination of the Japanese Institute for Cancer Research. Only the years of meeting together, with the resultant development of mutual scientific respect and personal friendship, could lead to the acceptance of a mutual protocol, forms, and statistical analysis. This protocol is currently accessioning patients successfully and will, hopefully, be the cornerstone for a wide range of collaborative clinical studies under the U.S.-Japan Cooperative Cancer Research Program in the second five years.

Future Directions

In the future, all of the treatment aspects formerly scattered among other aspects of the Program will be brought together. In the next five years, progress will continue both along modality-oriented lines and along disease-oriented lines, with the two blending together where appropriate

The modality thrusts will involve chemotherapy, radiation therapy, and immunotherapy. In chemotherapy, the vigorous exchange of drugs for both preclinical and clinical testing will continue. Emphasis will remain on new antitumor antibiotics and other natural products and on the four analogue areas of bleomycins, anthracyclines, nitrosoureas, and fluoropyrimidines. In radiation, the exchange of information on the High Linear Energy Transfer technique in both countries will continue. In addition, a dialogue will begin on other new developments in radiation oncology such as radiation sensitizers, hyperthermia, the interaction of drugs and radiation, and new fractionation schedules. In immunotherapy, there will be continued exchange of information on new immune modulations approaches. Disease-oriented approaches will focus initially on four tumors in which some exchange has already taken place. These are gastric cancer, breast cancer, lung cancer, and bladder cancer. In each of these diseases there will be an attempt to integrate the modality-oriented developments.

Gastric cancer will be a continuing focus. As new drugs are developed in each country, gastric cancer will be an important disease for Phase II testing. This will be particularly true in Japan where this tumor is such a major killer. Any new active drugs uncovered will then be integrated into combination regimens with other active drugs such as mitomycin-C, adriamycin, 5-FU, and methyl CCNU. The impetus begun with the current U.S.-Japan protocol for advanced disease will continue with new mutually developed protocols based on the current status of the clinical research. Discussions will also be held about a joint surgical adjuvant trial in which drugs will be given after curative resection for those patients at high risk for recurrence.

Breast cancer is a disease in which many exciting developments in treatment are taking place. In the area of local and regional control, there are the developments of effective treatments which have better cosmetic results than classical radical mastectomy. These include the approaches for excisional biopsy and radiation. Adjuvant chemotherapy continues to be an area of high clinical research interest. Future developments will involve integration of the hormone receptor assay and hormonal therapy into the use of effective drug treatments. This will be an area where both chemotherapy and radiation therapy can be brought together with breast surgery to explore the possibility of joint trial between the two countries.

In the area of lung cancer, the combined modality treatment of small cell anaplastic (oat-cell) lesions - is resulting in high-response ratios and significant prolongation of survival. Radiation is used to help control the primary lesion and to prophylactically attack any relapse. Drug combinations are used to aid local control and to achieve metastatic cell kill. The interaction of drugs and radiation is a crucial area of study and a high priority area for a joint U.S.-Japan symposium. Again, it is hoped that collaborative studies would ultimately result.

In non-oat cell lesions, surgical resection has some curative potential and this is a prime area for the testing of adjuvant immunotherapy. The drug treatment is currently poor, and emphasis needs to be placed on finding new effective drugs. Both countries will be undertaking Phase II studies and the sharing of results will lead to rapid movement into further clinical study of any new drug found to be active.

CONFERENCE REPORTS

U.S.-JAPAN JOINT SYMPOSIUM ON PHASE I AND II IN CANCER CHEMOTHERAPY*

June 5-6, 1978

Keidanren Kaikan, Tokyo

AGENDA

Monday, June 5

9:00 a.m.	Welcome	**Dr. Yoshio Sakurai**
9:10 a.m.	**I. THE METHODOLOGY**	
	Chairman: **Dr. Michael Friedman**	
	1. Phase I Trials with a New Drug	
	U.S.A. — The Design of Phase I Clinical Trials	**Dr. Marcel Rozencweig**
	Japan — The Methodology of Phase I Trials	**Dr. Makoto Ogawa**
9:50 a.m.	**2. Phase II Trials with a New Drug**	
	U.S.A. — Methodology of Phase II Trials	**Dr. Franco M. Muggia**
	Japan — Phase II Study: Including Signal Tumors and Evaluation Criteria	**Dr. Hisashi Majima**
10:30 a.m.	Discussion	
10:40 a.m.	COFFEE	
10:55 a.m.	**II. THE CLINICAL EVALUATION OF ANALOGUES**	
	Chairman: **Dr. Franco M. Muggia**	
	U.S.A. —	**Dr. Stephen K. Carter**
	Japan — Clinical Evaluation of Ara-C Analogues	**Dr. Kazumasa Yamada**
12:10 p.m.	LUNCH	

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*Sponsored by the National Cancer Institute (U.S.A.) and the Japan Society for the Promotion of Science; organized by Drs. Stephen K. Carter, Yoshio Sakurai, and Franco M. Muggia.

Monday, June 5 (continued)

2:00 p.m. **III. CLINICAL EVALUATION STRATEGY IN SPECIFIC DISEASE TYPES**

Chairman: **Dr. John Macdonald**

1. Lung

U.S.A. — **Dr. Robert Comis**

Japan — Present Status of Chemotherapy of Lung Cancer in Japan **Dr. Kazuo Ota**

2:50 p.m. **2. Breast**

U.S.A. — **Dr. Robert Benjamin**

Japan — Present Situation of Chemotherapy for Breast Cancer in Japan **Dr. Hiroki Koyama**

3:55 p.m. Chairman: **Dr. Stephen K. Carter**

3. Gastrointestinal

U.S.A. — Clinical Evaluation Strategy in Gastrointestinal Cancer **Dr. John Macdonald**

Japan — Clinical Study on Chemotherapy of Gastrointestinal Cancer (in one institute of Japan) **Dr. Tatuo Saito**

4:45 p.m. **4. Genitourinary**

U.S.A. — Clinical Evaluation Strategy in Genitourinary Cancer **Dr. Michael Friedman**

Japan — Recent Results in the Treatment of a Metastatic Cervical Cancer with a Sequential Combination of Bleomycin and Mitomycin C **Dr. Tadaoki Miyamoto**

5:35 p.m. Discussion

6:00 p.m. Adjourn

Tuesday, June 6

9:00 a.m. **IV. NEW DRUGS**

Chairman: **Dr. Yoshio Sakurai**

1. The New NCI Screen and Its Implication for Clinical Evaluation **Dr. Abraham Goldin**

Discussion

Tuesday, June 6 (continued)

9:30 a.m.	Chairman: **Dr. Abraham Goldin**	
	2. Natural Products under Development	
	U.S.A. —	**Dr. John D. Douros**
	Japan —	**Dr. Hamao Umezawa**
	Discussion	
10:20 a.m.	COFFEE	
10:35 a.m.	Chairman: **Dr. Hamao Umezawa**	
	3. New Drugs in Clinical Trials	
	U.S.A. — New Drugs in U.S.A.	**Dr. Franco M. Muggia**
	Japan — Effect and Mode of Action of N^4-Acyl Cytosine Arabinoside	**Dr. Yoshio Sakurai**
	Discussion	
11:25 a.m.	**V. FOUR SPECIFIC SESSIONS ON DRUG CLASSES OF INTEREST**	
	Chairman: **Dr. John D. Douros**	
	1. Nitrosoureas	
	U.S.A. — Nitrosoureas of Clinical Interest in Gastrointestinal Cancer	**Dr. John Macdonald**
	Japan — Further Phase II Study on ACNU	**Dr. Tatuo Saito**
	Experimental Studies on Nitrosourea Derivatives in Japan	**Dr. Shigeru Tsukagoshi**
	Discussion	
12:25 p.m.	LUNCH	
2:00 p.m.	Chairman: **Dr. Marcel Rozencweig**	
	2. Bleomycins	
	U.S.A. —	**Dr. Robert Comis**
	Japan — Phase II Study of Pepleomycin: New Synthetic Bleomycin	**Dr. Tsuyoshi Miura**
	Discussion	

Tuesday, June 6 (continued)

2:50 p.m. Chairman: **Dr. Robert Comis**

3. Anthracyclines

U.S.A. — **Dr. Robert Benjamin**

Japan — Clinical Experiences on Aclacinomycin: Phase I and II, including Toxicity and Irradiation-drug Effects **Dr. Hisashi Majima**

Discussion

3:40 p.m. COFFEE

3:55 p.m. Chairman: **Dr. Robert Benjamin**

4. Fluorinated Pyrimidines

U.S.A. — New Strategy in Fluorinated Pyrimidines **Dr. Michael Friedman**

Japan — Phase I and Early Phase II Study on FD-1 and HCFU **Dr. Tetsuo Taguchi**

Discussion

4:55 p.m. **VI. THE U.S.-JAPAN JOINT GASTRIC CANCER PROTOCOL**

Chairman: **Dr. Stephen K. Carter**

Japan — **Dr. Makoto Ogawa**

U.S.A. — **Dr. Michael Friedman**

5:35 p.m. SUMMARY AND CLOSING REMARKS **Dr. Stephen K. Carter**

6:00 p.m. Adjourn

Wednesday, June 7 (Palace Hotel)

9:30-11:30 a.m. BUSINESS MEETING: Chemotherapy

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ANALYTICAL EPIDEMIOLOGY PROGRAM AREA REPORT

54A

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Program Coordinators:
Dr. T. Hirayama
Dr. R. W. Miller

ANALYTICAL EPIDEMIOLOGY PROGRAM AREA REPORT

October 1, 1977 to September 30, 1978

Administrative Report

The following is a listing of the past year's activities, which includes Meetings, Seminars, and Conferences; the Exchange of Scientists; and the Exchange of Materials.

MEETINGS, SEMINARS, AND CONFERENCES

The Japan-U.S. Conference on Biostatistics in the Study of Human Cancer was held at the Radiation Effects Research Foundation (RERF) in Hiroshima, May 22 to 25, 1978. Eight visitors from the United States, others from the RERF, and about 40 Japanese attended this rare interaction of statisticians and physicians (mostly epidemiologists). The purpose of the conference was to seek fresh views on medical statistics (scientific design and data analysis) as it relates especially to oncology. In Japan there has been no tradition of biostatistics among mathematicians. The conference may have encouraged developments between the two countries in this regard. As a next step, two biostatisticians in oncology, one of them a physician, are to be asked to participate in an international conference on "Information Systems," to be held in Tokyo during the summer of 1979.

After the Hiroshima conference, five of the U.S. biostatisticians gave a one-day symposium at the Fukuoka Medical College, two spoke at the Institute of Statistical Mathematics in Tokyo, and one each spoke at Kawasaki University in Kurashiki, Nagoya University, Osaka University, the Adult Health Center in Osaka, Chiba University, and Tokyo University. There was a substantial exchange of biostatistical viewpoints during these visits.

EXCHANGE OF SCIENTISTS

1. Saketami Tominaga, M.D., Chief of the Division of Epidemiology at the Aichi Cancer Research Institute, spent one month in the United States during September 1977. He visited several centers for cancer epidemiology, including the Johns Hopkins University School of Public Health, the American Health Foundation in New York, the National Cancer Institute (NCI), and the Cancer Center in Honolulu.
2. A group of four U.S. biostatisticians served as visiting scientists (see Meetings, Seminars, and Conferences above). They were James E. Grizzle, Ph.D., Professor and Chairman, Department of Biostatistics at the University of North Carolina, School of Public Health; Edmund A. Gehan, Ph.D., Chief, Department of Biomathematics, M.D. Anderson Cancer Center; David G. Hoel, Ph.D., Chief, Biometry Branch and Acting Scientific Director, National Institute of Environmental Health Sciences; and John J. Gart, Ph.D., Head, Mathematical Statistics and Applied Mathematics Section, National Cancer Institute (NCI).

EXCHANGE OF MATERIALS

1. A sample of preserved mixed vegetables ("pickles") from Linhsien County, China, suspected of containing a carcinogen related to concurrent epidemics of esophageal cancer in man and gullet cancer in chickens, were brought by Dr. R. W. Miller to the laboratories of Dr. T. Sugimura to be tested in the Ames system. The test was positive, indicating the presence of a mutagen/carcinogen. The active principle could be isolated if a large sample of "pickles" were available, but so far such a sample has not been available.
2. The Chinese claimed that cigarette smoking was not carcinogenic in the People's Republic. Sample packs of two brands of Chinese cigarettes brought by Dr. Miller to Dr. Sugimura for Ames testing proved to be as mutagenic as European, Japanese or American cigarettes. Thus, the Chinese have not happened upon a safe cigarette.
3. Lyophilized urine specimens from several U.S. families with high frequencies of specific cancers have been sent from the Clinical Epidemiology Branch, NCI, to Dr. Sugimura for Ames testing. So far, one family with four children and three other relatives with acute myelogenous leukemia and possible DNA repair defect, has shown questionably abormal Ames test results. Repeat specimens have been sent to Tokyo. Another family had urinary bladder cancer in three generations, and a third family had five members with renal cell carcinoma.

FUTURE MEETINGS

It is possible that two U.S. computer experts in medicine/oncology will be sent to participate in an international conference in Tokyo in the Summer of 1979 (see Meetings, Seminars, and Conferences above).

Scientific Summary of Program Area

SUMMARY OF YEAR'S ACTIVITIES

1. The Japanese side published a volume on cancer morbidity in the United States and Japan (see Publications following).
2. A binational and multidisciplinary dialogue of physician-oncologists and statisticians may have been initiated.

SPECIFIC OBJECTIVES TO BE ACCOMPLISHED

1. Further encouragement of biostatistical exchanges.
2. New interactions between epidemiologic and laboratory research on carcinogenesis under the reorganized U.S.-Japan Cooperative Cancer Research Program, which brings both under the same overall leadership.

COOPERATIVE ACTIVITIES RESULTING FROM PAST MEETINGS

1. See Meetings, Seminars, and Conferences above.
2. Takashi Yanagawa, D.Sc., a statistician, completed a year as a Visiting Scientist (sponsored by National Institutes of Health (NIH) in the United States) in the Environmental Epidemiology Branch. He has returned to the Department of Mathematics at Kyushu University, where he played an important role in arranging for the conference described in Meetings, Seminars, and Conferences above. He apparently developed a substantial interest in medical statistics while at the National Cancer Institute.

Publications

1. Hirayama, T., ed., *Comparative Epidemiology of Cancer in the U.S. and Japan: Morbidity*. Japan Society for the Promotion of Science, Tokyo, May 1978, 107 pages.
2. "Proceedings of the Japan-U.S. Conference on Biostatistics in the Study of Human Cancer." *Environmental Perspectives*. In press.

SUMMARY OF FUTURE PROGRAM DEVELOPMENTS

In addition to the Program developments described above, many new interdisciplinary activities will be pursued under the new reorganized binational program.

Five Year-Summary Report

SUMMARY OF ACTIVITIES AND ACCOMPLISHMENTS

The U.S.-Japan Cooperative Cancer Research Program was established in May 1974. Except for the Chairmen, its Committee on Analytical Epidemiology has varied in membership from meeting to meeting in accord with the subject under discussion.

Host Susceptibility

During a visit to Japan on May 18, 1974, Dr. Robert Miller met in Tokyo with Dr. Takeshi Hirayama and other epidemiologists for a one-day symposium concerning the Japan Childhood Tumor Registry. Between 1969 and 1973, and continuing since then, this Registry recorded about 1000 new cases each year in six large metropolitan areas.

During the visit, Dr. Miller learned in advance that the Japanese planned to send 20 middle-level academic physicians annually to the United States for up to three months each. To make the most of this opportunity, it was agreed that Dr. Keiko Ohmi, a pediatric oncologist at Tokyo University who attended the one-day symposium, would be the first exchange scientist under the Program's Committee on Analytical Epidemiology. She would concentrate on family cancer studies as a source of clues to new understanding of the fundamental biology of cancer. The approach, although productive in the United States, was not widely applied there because it did not come easily to clinicians. In Japan, there appeared to be much wider susceptibility to the concept. Dr. Ohmi learned a great deal about U.S. oncology in general during her two month stay in early 1975 in the Epidemiology Branch, NCI. She also visited five pediatric cancer centers in other cities. The characteristic heavy case-load of hospital physicians in Japan permitted only limited application of the etiological research approaches she observed at the NCI.

A second opportunity to develop bedside etiologic studies arose later in the year when a conference on the genetics of human cancer was held in Orlando, Florida, December 2 to 4, 1975. The sessions were attended by about 100 persons, including Dr. Hirayama, six other Japanese epidemiologists, and the U.S.-U.S.S.R. Joint Working Group on Mammalian Somatic Cell Genetics Related to Neoplasia. After the conference, a one and one-half day symposium was held in Orlando, Florida, for the U.S.-Japan Committee on Analytical Epidemiology. The title, "Precious Cases for Epidemiological Studies," was suggested by Dr. Hirayama. Substantial information was exchanged, which affected future directions of the Committee and of individual participants. In particular, the concepts of family studies and host susceptibility seem more likely to gain ground through clinicians and laboratory scientists than through classical epidemiologists.

Environmental and Demographic Studies

Meanwhile, Dr. Hirayama was invited to participate in a three-day conference sponsored primarily by the Epidemiology Branch, NCI, in Key Biscayne, Florida, on December 10 to 12, 1974. This meeting led to the publication of its very well received proceedings, "Persons at High Risk of Cancer," which has become a handbook on environmental cancer epidemiology. Also at the meeting was Dr. M. Hitosugi, an environmental epidemiologist, who worked with Dr. Hirayama's group and has since moved to Kitasato University. Dr. Hitosugi's attendance took place during his six-month appointment as a visiting scientist in the Epidemiology Branch, NCI, beginning in October

1974, under the sponsorship of another binational program (the Panel on Environmental Mutagenesis and Carcinogenesis of the U.S.-Japan Cooperative Medical Science Program). Dr. Hitosugi has had an extraordinary exposure to developments in U.S. cancer epidemiology during the six-month period and during his attendance at the conference, both in the field of environmental cancer and in the field of genetics of human cancer.

On February 22, 1975, during a visit to Japan, Dr. Miller met for several hours with Dr. Hirayama and with four epidemiologists from elsewhere in Japan to discuss recent developments in epidemiology in each country. Special emphasis was placed on the desirability of comparing cancer mortality maps by county (or health care districts) in Japan with those being produced at the National Cancer Institute (NCI). Such maps have since been issued by both countries, and were independently "invented" in the People's Republic of China, where cancer mortality for specific anatomic sites is being mapped by commune for seven Provinces.

On May 4, 1976, Dr. Hirayama met in Bethesda, Maryland, with Dr. Miller to discuss future activities of the Committee. In preparation for its meeting in October, Dr. Hirayama requested that, by August 1976, data be provided to him on age-specific and sex-specific mortality rates for U.S. whites and blacks annually, 1950-1974, to be compared with Japanese data. Tapes, microfiche, and tabulations were hand carried to Tokyo in August by Dr. Miller, who was attending a meeting there. Dr. Hirayama has since published the data as a book on cancer mortality issued by the Japan Society for the Promotion of Science (see Publications below). He has also used published U.S. data on cancer morbidity as compared with Japanese data for a publication under the same auspices (see Publications below).

The second exchange scientist under the Program was Dr. T. Kawana, an obstetrician-virologist from Tokyo University interested in comparing infection with herpesvirus type-2 in uterine vaginal cancer in Japan and in the U.S. He spent a productive three months each at Johns Hopkins and at Emory Universities beginning in February 1975.

On October 8 and 9, 1975, Dr. Kawana reported at a Tokyo meeting of the Committee that differences between the findings in the two countries in addition to other evidence, indicated that herpesvirus infection cannot account for a substantial proportion of cases of uterine cervical cancer. At the meeting, Dr. Hirayama presented the graphs for cancer mortality by age, sex, calendar time, and race (whites, blacks, Japanese) based in part on unpublished U.S. data especially obtained and brought to him two months earlier.

The U.S. participants consisted of five scientists who were already in Japan for other reasons. In accord with their interests, a comparison was made of the etiologies, insofar as they are known, of leukemia, uterine cervical cancer, and urinary bladder cancer. Epidemiologic and laboratory evidence indicated that chromosomal abnormalities were associated with leukemia, that uterine cervical cancer seems to be horizontally transmitted as a venereal disease, and that bladder cancer is largely due to chemicals and cigarette smoking. The epidemiologic contrasts of these three cancers is marked, and indicates dissimilar origins.

The meeting generated several important questions or comments, which arose largely through the intermingling of scientists from different specialities. Of particular interest was the observation that the Japanese are "resistant" to five forms of lymphatic disease: chronic lymphocytic leukemia, lymphosarcoma, infectious mononucleosis, lymphoma after immunosuppression for renal transplantation, and Hodgkin's disease early in life that gives rise to the first of the bimodal age-peaks, absent in Japan but seen in all other countries. The sixth Japanese exchange scientist under the Program, Dr. T. Miyake, an epidemiologist from Sapporo Medical College, has a special interest in leukemia, and discussions will be held with him on the above peculiarities of occurrence when he visits the United States for one month beginning late September 1978.

Biostatistical Innovations

Apart from the staff of the Radiation Effects Research Foundation (RERF) in Hiroshima, Japan (formerly the Atomic Bomb Casualty Commission), U.S. biostatisticians are seldom involved with activities in Japan. Traditionally, Japanese statisticians have not been concerned with biology or medicine, thus accounting for the near absence of contact between the two countries in biostatistics.

Early in 1975, Dr. Miller initiated inquiries about the possibility of a conference of U.S. and Japanese biostatisticians. As a first step in this direction, Dr. William J. Blot, a biostatistician in the Epidemiology Branch, National Cancer Institute (NCI), spent three weeks at various Japanese research centers in October 1975 describing his specialty as it is applied in the United States. A spark of interest was struck in Dr. A. Kudo, a mathematical statistician at Kyushu University, who had spent several years in the United States using his creative mathematical talents in genetics and other biomedical subjects.

A second step involved the appointment of Dr. T. Yanagawa, a Ph.D. and a student of Dr. Kudo, for one year as a visiting scientist, sponsored by the NIH, under the direction of Dr. Blot at the National Cancer Institute (NCI). Dr. Yanagawa researched publications on biostatistics, wrote several papers on his ideas about them, and later helped immensely in planning the U.S.-Japan conference on biostatistics.

Japanese leaders in statistics agreed to participate, and the conference was organized by Drs. Kudo and Blot. Sponsorship by the Japanese side of the U.S.-Japan Cooperative Cancer Research Program depended on including medical epidemiologists, a wise decision.

The meeting was held at the Radiation Effects Research Foundation (RERF) on May 22 to 25, 1978, in Hiroshima. Seven biostatisticians and one epidemiologist attended from the United States, plus others from the RERF. About 25 Japanese mathematicians and medical epidemiologists attended in addition to those from RERF. Among them were an impressive group of Japanese "alumni" of a Visiting Scientist Program of ABCC/RERF sponsored by the NCI, under which several young physicians or statisticians each year came from government or universities to spend two months in the United States at a summer session on statistics or epidemiology at a School of Public Health, and ten months at the RERF in cancer epidemiology.

We learned at the conference that statistics as an independent discipline has not developed in Japan as it has in the United States, where over 190 universities offer graduate degrees in this field, and where about 35 universities specialize in biostatistics. In Japan no such degrees are offered, but mathematical statistics is taught at several universities. Not only did U.S. and Japanese statisticians meet for the first time, but so did physicians and statisticians within Japan, who found that they had interests in common. The meeting revealed that opportunities for statisticians in cancer research vary according to sub-area. Ingenuity can be vigorously tested in studies related to animal models, and essentially all recent advances in studies of human cancer survival data have come from biostatistics. By contrast, case-control studies require statisticians for proper planning and analysis, but not for statistical invention at this time.

After the conference, the U.S. biostatisticians served as short-term visiting scientists by speaking at eight academic centers. Three of the visitors expressed a desire to have young Japanese on fellowships in their departments. The Japanese senior statisticians in turn have asked if the United States can cover the expenses of two U.S. computer experts (one medical, one non-medical) to participate in an international conference on information systems in Tokyo to be held for a few days in the summer of 1979. After the conference the two computer experts would serve as exchange scientists for a short time at several universities. It is of interest that medical uses of the computer are being included in this conference organized by Japanese mathematicians.

Interaction of Epidemiology and Laboratory Research

New clues to the cause and prevention of cancer can come from clinical, epidemiological, or laboratory observations, but progress tends to be most rapid when the three research approaches interact with one another. Recently there has been such an exchange between the Clinical Epidemiology Branch of the NCI and Dr. Sugimura's laboratory. Pickles thought to be related to parallel epidemics of cancer of the esophagus/gullet in people and chickens of Linhsien County, China, were brought by Dr. Miller to Dr. Sugimura's laboratory for testing in the Ames system. They proved to be mutagenic, and may therefore also be carcinogenic. As yet, additional samples have not been available for isolation of the active principle. Two brands of Chinese cigarettes have been Ames-tested by Dr. Sugimura's group to determine if the claim that lung cancer is not related to smoking is due to a lack of carcinogens in their cigarettes. It is not, for the cigarettes were just as mutagenic as those made elsewhere in the world. Lyophilized urine specimens from several families heavily affected by specific cancers and under study by Dr. Miller's group have been sent to Tokyo for Ames testing by Dr. Sugimura's staff. In one family so far, the results were thought to be abnormal. The test is being repeated on new specimens.

EXCHANGE OF SCIENTISTS

The following Japanese scientists visited their counterparts in the United States.

February to March 1975: Dr. Keiko Ohmi, a pediatric oncologist from the Department of Pediatrics at Tokyo University, spent two months in the Epidemiology Branch, National Cancer Institute (NCI), learning about clinical aspects of epidemiology especially as they relate to family cancers. She also observed the U.S. style of chemotherapy and psychological aspects of childhood leukemia. She visited the pediatric oncology units at Memorial Hospital in New York, Cincinnati Children's Hospital, St. Jude Hospital, the M.D. Anderson Hospital, and the Texas Children's Hospital in Houston.

February to July 1975: Dr. T. Kawana, an obstetrician-virologist at Tokyo University, worked in the laboratories of Dr. L. Aurelian at Johns Hopkins University and Dr. A. Nahmias at Emory University studying infection with herpesvirus type-2 in relation to cancer of the uterine cervix in Japan as compared with the U.S.

July to December 1975: Dr. K. Fukuda, an epidemiologist from Sapporo University, spent six months with Dr. T. Hirohata in the Department of Epidemiology at the University of Hawaii School of Public Health in studies of epidemiologic methods.

March 29 to April 28, 1977: Dr. M. Nagao, a biochemist from the National Cancer Research Institute in Tokyo, spent two weeks in the Clinical Epidemiology Branch, National Cancer Institute (NCI), and two weeks with Dr. K. Nakanishi at Columbia University to discuss case-ascertainment for studies using the Ames test and sister-chromatid exchange evaluation as measures of mutagenicity/carcinogenicity and to demonstrate her methods for heightening the sensitivity of the Ames test.

September 13 to October 12, 1977: Dr. S. Tominaga, from his new position as Chief, Division of Epidemiology, Aichi Cancer Center Research Institute, visited several centers for cancer epidemiology in the U.S. for background in developing plans for his program in Nagoya.

September 25 to October 24, 1978: Dr. H. Miyake, Professor of Public Health at Sapporo Medical College, will visit Roswell Park Memorial Institute in Buffalo and the National Cancer Institute (NCI) to discuss the epidemiology of leukemia and methods for teaching the subject.

The following U.S. scientists visited their counterparts in Japan:

October 1975: Dr. William J. Blot, a biostatistician in the Epidemiology Branch, NCI, spent three weeks discussing and lecturing on the importance of biostatistics in biomedical research, with special reference to oncology. He visited the National Cancer Center Research Institute, the Institute for Statistical Mathematics, the Institute of Public Health (all three in Tokyo), the Department of Preventive Medicine of Kitasato University, the Department of Public Health of Sapporo Medical College, the Department of Epidemiology of Aichi Cancer Center, the Adult Health Center in Osaka, the Radiation Effects Research Foundation in Hiroshima, the Department of Public Health and Mathematics at Kyushu University, and the Department of Human Genetics at the National Institute of Genetics in Mishima. The trip laid the groundwork for a binational conference three years in the future.

May 22 to 31, 1978: Four U.S. biostatisticians visited Japan along with four other U.S. participants in a Japan-U.S. Conference on Biostatistics in the Study of Human Cancer, May 22 to 25, 1978. After the Conference they visited singly, in pairs, or as a group, the Fukuoka Medical College, the Adult Health Center in Osaka, Osaka University, Nagoya University, Chiba University, and the Institute for Statistical Mathematics in Tokyo. Seminars or lectures were given at each place during the interval of May 27 to 31, 1978.

PUBLICATIONS

1. Hirayama, T., ed., *Comparative Epidemiology of Cancer in the U.S. and Japan: Mortality*. The U.S.-Japan Cooperative Cancer Research Program. January 1977, pp. 122.
2. Hirayama, T., ed., *Comparative Epidemiology of Cancer in the U.S. and Japan: Morbidity*. Japan Society for the Promotion of Science, Tokyo, May 1978, pp. 107.
3. "Proceedings of a Japan-U.S. Conference on Biostatistics in the Study of Human Cancer." *Environmental Perspectives*. In press.

FUTURE DEVELOPMENTS

Future exchanges of scientists in biostatistics and computer technology as related to cancer research are contemplated, along with a continued exchange of medical epidemiologists. A greater interaction of epidemiology and laboratory research is anticipated under the reorganized binational program.

BEST DOCUMENT AVAILABLE

BREAST CANCER
PROGRAM AREA REPORT

BEST DOCUMENT AVAILABLE

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Program Coordinators:
Dr. Nathaniel I. Berlin
Dr. Haruo Sugano

BREAST CANCER PROGRAM AREA REPORT

September 1977 to October 1978

Administrative Report and Scientific Summary

MEETINGS, SEMINARS, AND CONFERENCES

The Annual Meeting of the Breast Cancer Program Area and a symposium entitled "Hormones, Receptors, and Breast Cancer" were held in Honolulu, Hawaii, on March 6 and 7, 1978. The proceedings of this symposium were published as the monograph *Progress in Cancer Research and Therapy: Hormones, Receptors, and Breast Cancer*, 1978 (see Conference Reports following this Program Area Report).

The symposium was organized by Dr. W.L. McGuire, University of Texas, and Dr. K. Matsumoto, Osaka University, and addressed two major subjects: Session I: Hormones and Receptors in Human Breast Cancer in Japan and the United States; and Session II: Basic Studies on Endocrine Therapy in Breast Cancer.

Scientific results obtained were as follows:

Hormones and Receptors in Human Breast Cancer in Japan and the U.S.A.—Investigations of 1,000 Japanese and 1,000 American Patients

In Japan, the incidence of breast cancer is remarkably lower than in the United States. Japanese breast cancer patients have a better survival rate than American breast cancer patients. However, the survival advantage of Japanese patients cannot be explained by tumor estrogen (ER) and progesterone (PgR) receptor incidence, since the incidence was slightly lower in Japanese patients than in American patients. The slightly lower incidence in Japan is due mainly to the significantly lower incidence of ER in postmenopausal Japanese (55 percent) than in postmenopausal American patients (75 percent). In both countries, the response rates to endocrine therapies were 50 to 70 percent for ER+ and/or PgR+ tumors, and less than 10 percent for negative tumors. Assays of ER and/or PgR were shown to be useful markers for predicting the response to endocrine therapy.

Basic Studies on Endocrine Therapy in Breast Cancer

Antiestrogens such as tamoxifen and epitiostanol (Shionogi Company) were shown to be useful materials for endocrine therapy in breast cancers. Basic mechanisms of antihormone action of these antiestrogens were shown and discussed.

The growth of mammary tumors induced in rats (DMBA-tumors) and mice (pregnancy-dependent tumors) was shown to be dependent upon the action of multiple hormones such as prolactin and estrogen. However, growth of Shionogi carcinoma in mice was stimulated only by androgens. These animal tumors are thought to be adequate model tumors for investigating endocrine therapy in human breast cancer.

The following problems remain to be investigated in the future:

Difference of ER Incidence Between Postmenopausal Japanese and American Breast Cancer Patients

The incidence of breast cancer is much higher in the postmenopausal American than in the premenopausal American and in both premenopausal and postmenopausal Japanese patients. Investigations seeking an explanation of the difference in ER incidence would seem to be valuable, in order to determine the pathogenesis of some human breast cancers.

Tumor Hormone Receptors and Response to Endocrine Therapy

ER- was shown to be a good marker for selecting endocrine-resistant tumor. However, about 30 to 50 percent of ER + and/or PgR + tumors were endocrine-resistant tumors. Investigations on various receptor systems are required in order to obtain ideal markers for selecting endocrine-responsive tumors. The basic investigations using animal tumor models suggest that endocrine therapy may be more effective for controlling the growth of human breast cancers in the early stage of development. Extensive investigations on endocrine therapy for early breast cancer should be attempted in the near future.

Mechanism of Hormone Dependent Growth

The mechanism should be clarified in order to establish ideal endocrine therapy for human breast cancers.

Hormone Receptors and Histopathology

The relationship between ER, PgR, androgen, and prolactin receptors and histopathology should be examined in breast, endometrial, and prostate cancers.

The participants at this annual meeting and symposium found the presentations and discussions to be extremely stimulating and productive. Since there are great differences in the incidence and prognosis of breast cancer between Japanese and American patients, studies on breast cancers are very appropriate to the U.S.-Japan Cooperative Cancer Research Program. In this seminar, it was possible to clarify many important points on the endocrine control and endocrine therapy of breast cancer. In light of the important and rewarding exchange of information resulting from this seminar, it is hoped that cooperation between Japan and the United States in breast cancer research will continue into the future.

The presentations at this seminar have been published in a monograph, *Progress in Cancer Research and Therapy: Hormones, Receptors, and Breast Cancer*, Volume 10, pp. 1-369 (New York: Raven Press, 1978). Acknowledgements are given to the National Cancer Institute (NCI) and the Japan Society for the Promotion of Science. For a listing of the presentations, see Conference Reports following this Program Area Report.

EXCHANGE OF SCIENTISTS

1. Dr. Hiroki Koyama from the Osaka Adult Disease Center served as a visiting scientist with Dr. Carbone at Madison, Dr. Ahman at Rochester, Dr. Berlin at Chicago, Dr. Dao at Buffalo, Dr. Muggia at Bethesda, and Dr. Carter at San Francisco. Dr. Koyama also attended the annual meeting of the National Surgical Adjuvant Breast Project (NSABP) held in Miami. The purpose of his visit was to investigate the present status of chemotherapy for breast cancer in the United States and to discuss mutual problems of adjuvant and combined modality therapy for breast cancer. The itinerary for this visit follows this Program Area Report.
2. Dr. Robert Yonemoto from the City of Hope Medical Center, Duarte, California, planned to visit Hokkaido University and Cancer Institute, Tokyo, but due to unexpected personal reasons, the visit has been postponed until 1979.

EXCHANGE OF MATERIALS

A program for review of histopathological material on breast cancer in Japan has been developed by Dr. William Hartmann of Vanderbilt University, Nashville, Tennessee. As a result of this program, Dr. Goi Sakamoto visited the United States to collaborate on further histopathological slides to compare the difference in specimens between the American and Japanese patients.

Future Activities, 1978-1979

MEETINGS, SEMINARS, AND CONFERENCES

A seminar on "Breast Cancer Treatment" is being organized by Drs. N.I. Berlin, H. Sugano, S. Carter, and Y. Sakurai. The projected date and place will be February 26 and 27, 1979, at the Palace Hotel, Tokyo.

The purpose of this seminar is to clarify and compare the therapeutic effects of combined modality treatment on breast cancer in both countries. The subjects will be as follows:

- Comparison of Breast Cancer Among Japanese and American Females
- Screening for Breast Cancer
- Surgical Treatment
- Specific Chemotherapy for Breast Cancer
- Chemotherapy for Metastatic Breast Cancer and Adjuvant Chemotherapy
- Hormone Receptors and Therapy
- Animal Models for Breast Cancer
- Future Prospect of Chemotherapy for Breast Cancer.

An agenda and list of participants for this symposium may be found in Conference Reports following this Program Area Report.

A preliminary meeting is tentatively being planned on "Breast Cancer in the Atomic Bomb Survivors." This meeting is being organized by Dr. Donald E. Henson and Dr. Shoji Tokuoka for May or June, 1979, at the Department of Pathology, Vanderbilt University.

Dr. Donald E. Henson, National Cancer Institute (NCI), and Dr. Stuart C. Finch, Vice Chairman and Chief of Research, Radiation Effect Research Foundation (RERF, formerly ABCC) Hiroshima, have talked about the possibility of a joint study on breast cancer in victims of the atomic bomb in Hiroshima and Nagasaki under the cooperation of the NCI and RERF with close liaison to the U.S.-Japan Cooperative Cancer Research Program. The purpose of this study is to review the incidence and distribution of different histological types of breast cancer in persons exposed to radiation from the atomic bomb. The preliminary meeting is to take place in the United States, perhaps in Nashville in May or June 1979, and the pathological review will take place in Japan, perhaps in Hiroshima in late 1979 or early 1980. Funds for travel expenses for the participants will be provided by the U.S.-Japan Cooperative Cancer Research Program.

EXCHANGE OF SCIENTISTS

1. Dr. Robert Yonemoto from the City of Hope Medical Center, Duarte, California, is planning to visit Dr. Hiroshi Kobayashi, Hokkaido University, and Dr. Haruo Sugano, Cancer Institute, Tokyo, in June 1979.
2. Dr. Masayoshi Tokunaga, from Kagoshima University, has tentative plans to visit the National Cancer Institute, Bethesda, and Dr. W. Hartmann at Vanderbilt University.

EXCHANGE OF MATERIALS

Tentative plans are being made to exchange histological materials for newer classification schemes on breast cancer.

FIVE-YEAR SUMMARY REPORT

During the first five years of the Breast Cancer Research Program Area, information has been successfully exchanged between Japan and the U.S. through the meetings held in Japan, Hawaii, and the United States. A number of Japanese scientists have been invited to the Breast Cancer Task Force meetings held in the United States and this has served to provide them with a broadly based summary of work supported by the National Cancer Institute (NCI). There have been a number of visiting scientists, both from Japan to the United States and from the United States to Japan. There have been no specific research protocols initiated, although collaborative efforts have been started. Dr. Gilbert Friedell's collaborative efforts during this period did not arise from the cooperative group, but are an example of cooperative efforts that began in the last five years.

The past five years were a period of great cooperative activity. A system for the exchange of information on a regular basis has been developed. It has been possible to learn what types of cancer research are being accomplished in Japan, and precisely where breast cancer research is being carried out in Japan. All the participants have learned much about the characteristics of breast cancer in Japan. In turn, the Japanese investigators have gained real insight into breast cancer research in the United States.

A number of Japanese investigators have taken up leads, particularly in the hormonal receptor field, that came from work started in the United States. Excellent cooperative efforts were developed in basic and clinical research on breast cancer.

Other Collaborative Activities

BREAST CANCER TASK FORCE

The United States Breast Cancer Task Force (BCTF) has been involved in meetings on collaborative efforts in breast cancer with the U.S.-Japan Cooperative Cancer Research Program. Ongoing activities in breast biology and breast cancer, in particular, are usually reported to the Japan Mammary Cancer Society.

The Japanese coordinator for the society and the BCTF is:

Dr. Masao Fujimori
Saitama Cancer Center
Urawa, Japan

Several Japanese investigators have constituted working groups and have selected a coordinator for their group activities. In the mammary tumor virus area, cooperation with the BCTF is maintained through:

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CONFERENCE REPORTS

SYMPOSIUM: HORMONES, RECEPTORS, AND BREAST CANCER

Honolulu, Hawaii

March 6-7, 1978

AGENDA

March 6, 1978

Session I.
Hormones and Receptors in Human Breast Cancer in Japan and U.S.A.

8:45 a.m.	An Opening Address	**Dr. N. I. Berlin**
9:00 a.m.	ER and Endocrine Responsiveness	**Dr. Y. Nomura**
9:20 a.m.	ER and Endocrine Responsiveness	**Dr. E. DeSombre**
9:40 a.m.	ER and Endocrine Responsiveness	**Dr. J. Wittliff**
10:00 a.m.	ER and Endocrine Responsiveness	**Dr. M. Lippman**
10:20 a.m.	Discussion	
11:00 a.m.	PgR and Endocrine Responsiveness	**Dr. W. L. McGuire**
11:20 a.m.	PgR and Endocrine Responsiveness	**Dr. K. Matsumoto**
11:40 a.m.	Discussion	
12:00 noon	LUNCH	
1:30 p.m.	Receptors and Histopathology	**Dr. H. Sugano**
1:50 p.m.	Receptors and Histopathology	**Dr. P. Rosen**
2:10 p.m.	Discussion	
2:30 p.m.	Hormone Action in Tissue Culture	**Dr. W. L. McGuire**
2:50 p.m.	Hormone Action in Tissue Culture	**Dr. M. Lippman**
3:10 p.m.	Hormone Action in Tissue Culture	**Dr. B. Leung**
3:30 p.m.	Discussion	

March 7, 1978

Session II.
Basic Studies on Endocrine Therapy in Breast Cancer

9:00 a.m.	Mechanisms of Antihormone Action	**Dr. J. Clark**
9:20 a.m.	Mechanisms of Antihormone Action	**Dr. B. Katzenellenbogen**
9:40 a.m.	Discussion	
10:10 a.m.	Antihormones in Breast Cancer	**Dr. J. Kato**
10:30 a.m.	Antihormones in Breast Cancer	**Dr. E. DeSombre**
10:50 a.m.	Discussion	
11:20 a.m.	LUNCH	
1:00 p.m.	Steroid Metabolism in DMBA Tumors	**Dr. B. Tamaoki**
1:20 p.m.	Growth of DMBA Tumors by Hormones	**Dr. B. Leung**
1:40 p.m.	Discussion	
2:10 p.m.	Hormone Dependent Mouse Tumors	**Dr. A. Matsuzawa**
2:30 p.m.	Shionogi Carcinoma 115	**Dr. K. Matsumoto**
2:50 p.m.	Polyamines in Mammary Tissues	**Dr. T. Oka**
3:10 p.m.	Discussion	
3:40 p.m.	Closing Address	**Dr. H. Sugano**

PARTICIPANTS

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PRESENTATIONS AT THE SYMPOSIUM ON HORMONES, RECEPTORS, AND BREAST CANCER

The following reports were published in *Progress in Cancer Research and Therapy: Hormones, Receptors, and Breast Cancer*, Volume 10, edited by William L. McGuire, M.D. (New York: Raven Press, 1978, pp. 1-369).

Estrophilin and Endocrine Responsiveness of Breast Cancer
Eugene R. DeSombre, Geoffrey L. Greene, and Elwood V. Jenson

Clinical Usefulness of Estrogen Receptor Assay in Early and Advanced Breast Cancer
Y. Nomura, J. Yamagata, H. Kondo, K. Kanda, and K. Takenaka

Progesterone Receptors in Breast Cancer
William L. McGuire and Kathryn B. Horwitz

Progesterone and Estrogen Receptors in Japanese Breast Cancer
K. Matsumoto, H. Ochi, Y. Nomura, O. Takatani, M. Izuo, R. Okamoto, and H. Sugano

Hormone Receptors and Histopathology in Japanese Breast Cancer
H. Sugano, G. Sakamoto, A. Sakamoto, Y. Nomura, O. Takatani, and K. Matsumoto

Estrogen Receptor Protein (ERP) and the Histopathology of Human Mammary Carcinoma
Paul Peter Rosen, Celia J. Menendez-Botet, Ruby T. Senie, Morton K. Schwartz, David Schottenfeld, and Gist H. Farr

Studies of Steroid Hormone Effects on Human Breast Cancer Cells in Long-Term Tissue Culture
Jeannine S. Strobl and Marc E. Lippman

Mechanism of Action of Estrogen Antagonist: Relationship to Estrogen Receptor Binding and Hyperstrogenization
J. H. Clark, J. W. Hardin, S. A. McCormack, and H. A. Padykula

Basic Mechanism of Antiestrogen Action
Benita S. Katzenellenbogen

Epitiostanol, a Steroidal Anti-Estrogen Having Anti-Mammary Tumor Activity
Takashi Hori, Tamotsu Miyake, Ken'ichi Takeda, and Junzo Kato

Studies on the Antiestrogen CI628 in Relation to Breast Cancer
Eugene R. DeSombre and C. Richard Lyttle

Steroid Metabolism in Experimental Mammary Tumor Induced by 7,12-Dimethyl Benz(a) anthracene
Bun-ichi Tamaoki, Makoto Mori, Masatsugu Kitamura, and Takeshi Tominaga

Hormonal Dependency of Experimental Breast Cancer
Benjamin S. Leung

Cytoplasmic Progesterone Receptor in Mouse Mammary Tumors
Akio Matsuzawa, Tadashi Yamamoto, and Yukio Mizuno

In Vitro and *In Vivo* Studies in Androgen-Dependent Shionogi Carcinoma 115
K. Yamaguchi, B. Sato, S. Okamoto, Y. Kitamura, and K. Matsumoto

Polyamines in Growth and Development of Mammary Gland
Takami Oka, Tadashi Sakai, David W. Lundgren, and John W. Perry

Steroid Binding Proteins of Mammary Tissues and Their Clinical Significance in Breast Cancer
James L. Wittliff, Walter M. Lewko, Daniel C. Park, Timothy E. Kute, DeWitt T. Baker, Jr., and Leslie N. Kane

U.S.-JAPAN SEMINAR
ON
BREAST CANCER TREATMENT

Palace Hotel, Tokyo

February 26-27, 1979

Monday, February 26

9:30 a.m.	Session I	Chairman—**Dr. N. I. Berlin** Comparison of Breast Cancer Among Japanese and American Females **Dr. Goi Sakamoto**
10:00 a.m.	COFFEE	
10:30 a.m.	Session II	Chairman—**Dr. H. Sugano** Screening for Breast Cancer **Dr. Nathaniel I. Berlin** **Dr. Kenji Inoue**
11:30 a.m.	Session III	Chairman—**Dr. T. Kajitani** Surgical Treatment **Dr. William Donegan** **Dr. Keijiro Kuno**
12:30 p.m.	LUNCH	
2:00 p.m.	Session IV	Chairman—**Dr. Y. Sakurai** Specialities of Chemotherapy for Breast Cancer Clinical Aspect **Dr. Makoto Ogawa** Development of Drugs for Breast Cancer **Dr. Stephen Carter**
3:00 p.m.	COFFEE	

Monday, February 26 (continued)

3:30 p.m.	Session V	Chairman—**Dr. S. Carter** Chemotherapy for Metastatic Breast Cancer and Adjuvant Chemotherapy **Dr. Minoru Yoshida** **Dr. Kanji Kubo** **Dr. Osahiko Abe** Chairman—**Dr. H. Koyama** **Dr. William Donegan** **Dr. Masaru Izuo**
5:30 p.m.	Adjourn	
6:30-8:30 p.m.	Reception at Tsuru Room	

Tuesday, February 27

9:00 a.m.	Session V	Chairman—**Dr. W. Donegan** Chemotherapy for Metastatic Breast Cancer and Adjuvant Chemotherapy (continued) **Dr. Hiroki Koyama** **Dr. Douglas Tormey**
10:00 a.m.	COFFEE	
10:30 a.m.	Session VI	Chairman—**Dr. D. Tormey** Hormone Receptors and Therapy **Dr.Yasuo Nomura** **Dr. William McGuire** **Dr. Keishi Matsumoto**
12:00 noon	LUNCH	
1:30 p.m.	Session VII	Chairman—**Dr. W. McGuire** Animal Models for Breast Cancer **Dr. Takashi Tsuruo** **Dr. Osahiko Abe** **Dr. Daniel Griswold**
3:00 p.m.	COFFEE	

February 27 (continued)

3:30 p.m.		Chairman—**Dr. K. Matsumoto** **Dr. Hiroshi Nagasawa** **Dr. Y. S. Cho-Chung**
4:30 p.m.	Session VIII	Chairman—**Dr. N. I. Berlin** Future Prospect of Chemotherapy for Breast Cancer **Dr. Yoshio Sakurai** **Dr. Stephen Carter** **Dr. William McGuire**
5:00 p.m.	Closing Remarks and Adjournment	**Dr. Robert R. Omata** **Dr. Nathaniel I. Berlin** **Dr. Haruo Sugano**

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URINARY BLADDER CANCER PROGRAM AREA REPORT

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BEST DOCUMENT AVAILABLE

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Seminar on Clinical Evaluation, Multimodal Therapy, and Cooperative Studies of Bladder Cancer (Florida)

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- Participants 85

Program Coordinators:
Dr. George T. Bryan
Dr. Osamu Yoshida

URINARY BLADDER CANCER PROGRAM AREA REPORT

September 1, 1977 to December 31, 1978

Administrative Report

During this year's reporting period, the following activities took place.

MEETINGS, SEMINARS, AND CONFERENCES

The "Seminar on Clinical Evaluation, Multimodal Therapy, and Cooperative Studies of Bladder Cancer" was convened in Sarasota, Florida on December 10 to 13, 1978. A detailed report, including an agenda of the meeting and the participants, is presented in Conference Reports following this Program Area Report.

Following this meeting, the participants attended the "Annual National Bladder Cancer Project Investigators' Workshop," December 13 through 15, 1978.

EXCHANGE OF SCIENTISTS

The following Japanese scientists visited the United States during this reporting period as exchange scientists for the U.S.-Japan Cooperative Cancer Research Program:

1. Dr. Y. Ohno: Department of Preventive Medicine, Nagoya University School of Medicine visited Dr. A.S. Morrison, Harvard University School of Public Health, September 1977; and Dr. G.T. Bryan, University of Wisconsin Center for Health Sciences, October 1977.

The following scientists visited the following laboratories with support from other sources:

1. Dr. T. Iwasaki: Department of Urology, Faculty of Medicine, Kyoto University visited Dr. R. Oyasu, Department of Pathology, Northwestern University, June 1976 to October 1977.
2. Dr. Y. Hirao: Department of Urology, Nara Medical College visited Dr. R. Oyasu, Department of Pathology, Northwestern University, beginning October 1978.
3. Dr. S. Fukushima: Department of Pathology, Nagoya City University Medical School visited Dr. G. Friedell, Department of Pathology, St. Vincent Hospital, Worcester, beginning October 1977.
4. Dr K. Hirao: Department of Urology, Nara Medical College visited Dr. G. Friedell, Department of Pathology, St. Vincent Hospital, Worcester, December 1975 to August 1977.
5. Dr. S. Sugihara: Cancer Center, Nara Medical College visited Dr. J. Leighton, Medical College of Pennsylvania, Pennsylvania, June 1975 to June 1978.

6. Dr. M. Arai: Department of Pathology, Nara Medical College visited Dr. G. Friedell, Department of Pathology, St. Vincent Hospital, Worcester, September 1974 to October 1977.
7. Dr. Y. Kamiryo: Department of Urology, Faculty of Medicine, Yamaguchi University visited Dr. G.T. Bryan, University of Wisconsin Center for Health Sciences, August 1976 to August 1978.
8. Dr. N. Yamamoto: Department of Urology, Faculty of Medicine, Yamaguchi University visited Dr. G. T. Bryan, University of Wisconsin Center for Health Sciences, beginning August 1978.
9. Dr. M. Matsushima: Department of Urology, Toho Medical College visited Dr. G.T. Bryan, University of Wisconsin Center for Health Sciences, beginning August 1978.
10. Dr. T. Shirai: Department of Pathology, Nagoya City University Medical School visited Dr. C. King, Michigan Cancer Foundation, Michigan, beginning April 15, 1978.
11. Dr. M. Takahashi: Department of Pathology, National Institute for Public Health visited Dr. P. Shubik, The Eppley Institute, Nebraska, April 9, 1975 to April 26, 1977.
12. Dr. C.J. Grubbs: IIT Research Institute (IITRI), visited Dr. N. Ito, Department of Pathology, Nagoya City University Medical School, August 7, 1977 to August 21, 1977.
13. Dr. A.G. Lurie: University of Connecticut Health Center, Connecticut visited Dr. N. Ito, Department of Pathology, Nagoya City University Medical School, May 31, 1978 to June 16, 1978.

EXCHANGE OF RESOURCES AND MATERIALS

No extraordinary materials exchange has occurred this year. However, previous meetings and exchanges of scientists have permitted researchers in the U.S. and Japan to meet and become familiar with each others work. Through this direct scientist-to-scientist involvement, progress has been achieved for both sides.

Scientific Summary of Program Area

SUMMARY OF YEAR'S ACTIVITIES

This year was marked by individual bilateral personnel exchanges and planning for the forthcoming meeting. Personnel exchanges have continued and should result in future publications.

SPECIFIC OBJECTIVES ACCOMPLISHED

During this reporting period, the following objectives were accomplished:

1. A third bilateral meeting was planned
2. Bilateral scientist exchanges occurred
3. Exchanges of resources and materials continue
4. Joint publications are in progress.

COOPERATIVE AND COLLABORATIVE ACTIVITIES RESULTING FROM PAST MEETINGS AND DISCUSSIONS

1. Dr. N. Ito and Drs. G. Friedell and S.M. Cohen—through exchanges of personnel and materials.

2. Dr. M. Okada and Drs. C.C. Irving and G.T. Bryan—through exchanges of personnel and materials.

3. Dr. O. Yoshida and Dr. R. Oyasu—through exchange of personnel.

4. Dr. O. Yoshida and Dr. G.T. Bryan—through exchanges of personnel and materials.

5. Dr. Y. Ohno and Drs. A. Morrison and G.T. Bryan—through exchanges of personnel.

6. Dr. M. Ichikawa and Dr. G.T. Bryan—through exchanges of personnel and materials.

7. Dr. S. Sugihara and Dr. J. Leighton—through exchanges of personnel and materials.

8. Dr. N. Ito and Dr. C. King—through exchange of personnel.

9. Dr. M. Takahashi and Dr. P. Shubik—through exchanges of personnel.

Future Program Developments

A strong base of productive and collaborative basic and clinical science activities has been established in many interdisciplinary study areas dealing with bladder cancer. These include activities dealing with initiation and promotion, pathogenesis, epidemiology, detection, diagnosis, therapy, and rehabilitation. This base could be strengthened in future years to consolidate joint efforts initiated in these areas.

Five-Year Summary Administrative Report

MEETINGS, SEMINARS, AND CONFERENCES

1. "Experimental Models for Bladder Cancer," December 6 to 9, 1975, Honolulu, Hawaii
   Participants: 10 from the United States
   6 from Japan

2. "Etiology of Bladder Cancer," September 20 to 28, 1976, Kyoto, Japan
   Participants: 7 from the United States
   9 from Japan

3. "Clinical Evaluation Multimodal Therapy and Cooperative Studies of Bladder Cancer," December 10 to 13, 1978, Sarasota, Florida
   Participants: 19 from the United States
   11 from Japan

EXCHANGE OF MATERIALS

During the past five years, the Japanese have been most gracious in providing U.S. scientists with a large variety of chemicals for a variety of purposes. Of the many exchanges taking place, most occurred directly between the individual investigators.

EXTENT AND MANNER OF IMPACT OF ACTIVITIES

This program has enabled basic and clinical scientists possessing interests and skills in several areas dealing with bladder cancer to meet, exchange information, exchange scarce resources and collaborate on research programs. Effective bilateral personnel exchanges have occurred. These generally have been of the long-term variety and have resulted in collaborative published work. We owe a debt of gratitude to those sponsors who willingly and enthusiastically provided the resources of their laboratories and communities to these young scientists. Through these exchanges, we have successfully laid the groundwork for continuous collaboration throughout the careers of these individuals. This aspect has been most gratifying.

We anticipate that the U.S.-Japan Cooperative Cancer Research Program will lead to continuous interactive projects in many scientific areas dealing with bladder cancer. At least nine collaborative and cooperative activities of a continuous nature have been developed from past meetings and discussions. These include activities dealing with initiation and promotion of bladder cancer, and studies of pathogenesis, epidemiology, detection, diagnosis, therapy, and rehabilitation. It would be most unfortunate if the lines of communication that have been forged were allowed to decay because of changes of program emphasis.

Drs. O. Yoshida and G.T. Bryan expressed their pleasure in their participation, thereby helping to create a strong, viable program between Japan and the United States, and wish the U.S.-Japan Cooperative Cancer Research Program every success in the future.

CONFERENCE REPORTS

SEMINAR ON
CLINICAL EVALUATION, MULTIMODAL THERAPY, AND COOPERATIVE STUDIES OF BLADDER CANCER

Sarasota, Florida

December 10-13, 1978

Monday, December 11

8:30 a.m.	**OPENING SESSION – Dr. G. T. Bryan and Dr. O. Yoshida** Opening Statement of Goals and Purpose of Meeting
9:30 a.m.	**Comparison of Bladder Cancer in Japan and United States** CHAIRMAN: **Dr. W. F. Whitmore, Jr.**
9:30 a.m.	Epidemiology and Screening for Bladder Cancer **Dr. Alan Morrison**
10:00 a.m.	Morphological Comparison of Bladder Cancer in the U.S. and Japan **Dr. Nobuyuki Ito**
10:30 a.m.	COFFEE BREAK
11:00 a.m.	Pathology of Bladder Cancer **Dr. George M. Farrow**
11:30 a.m.	Discussion
1:00 p.m.	**Approaches to Therapy-Surgery** CHAIRMAN: **Dr. Nobuyuki Ito**
1:00 p.m.	Patient Selection **Dr. George R. Prout**
1:30 p.m.	Role of Curative Surgery **Dr. Takao Sonoda**
2:00 p.m.	Surgical Management **Dr. Willet F. Whitmore, Jr.**
2:30 p.m.	Partial and Radical Cystectomy **Dr. Yoshio Aso**
3:00 p.m.	Discussion

Monday, December 11 (continued)

3:15 p.m.	COFFEE BREAK
3:30 p.m.	**Approaches to Therapy-Radiation** CHAIRMAN: **Dr. George Prout**
3:30 p.m.	**Dr. Sachio Mochizuki**
4:00 p.m.	**Dr. Morris J. Wizenberg**
4:30 p.m.	Discussion

Tuesday, December 12

8:00 a.m.	**Approaches to Therapy-Chemotherapy and Immunotherapy** CHAIRMAN: **Dr. O. Yoshida**
8:00 a.m.	Approaches to Developing Effective Systemic Therapy **Dr. Mark Soloway**
8:30 a.m.	Chemotherapy and Immunotherapy in Japan **Dr. Tadao Niijima**
9:00 a.m.	Discussion
	COFFEE BREAK
9:30 a.m.	**Approaches to Therapy-Chemotherapy and Immunotherapy** CHAIRMAN: **Dr. Tadao Niijima**
9:30 a.m.	Chemotherapy for Metastatic Disease **Dr. Richard G. Hahn**
10:00 a.m.	Intravesical Therapy in Japan **Dr. Teruo Mishina**
10:30 a.m.	Intravesical Therapy and Cis-retinoic Acid **Dr. W. Koontz**
11:00 a.m.	Discussion
1:00 p.m.	**Design and Conduct of Clinical Trials and Collaborative Studies** CHAIRMAN: **Dr. Robert E. Greenfield**
1:00 p.m.	Clinical Studies in Japan **Dr. O. Yoshida**
1:30 p.m.	Planning and Organizing Collaborative Studies **Mr. Arthur G. Hilgar**

Tuesday, December 12 (continued)

2:00 p.m.	Design of Clinical Studies **Dr. George R. Prout**
	The Urologists Point of View **Dr. Kenneth Cummings**
	The Radiologists Point of View **Dr. William Shipley**
	The Chemotherapists Point of View **Dr. Albert Einstein**
	The Pathologists Point of View **Dr. George Penick**
3:40 p.m.	COFFEE BREAK
4:00 p.m.	The Statistical and Data Management Needs of Collaborative Studies **Dr. Sidney Cutler**
4:40 - 5:00 p.m.	Discussion

Wednesday, December 13

9:00 - 12:00 a.m.	**Strategies for Mutually Designed Clinical Studies** CO-CHAIRMEN: **Drs. O. Yoshida and G. T. Bryan**
	Discussion by all Participants

Wednesday evening through Friday (December 13-15, 1978)
ANNUAL NATIONAL BLADDER CANCER WORKSHOP — All Participants

MINUTES OF THE SEMINAR ON CLINICAL EVALUATION MULTIMODAL THERAPY AND COOPERATIVE STUDIES OF BLADDER CANCER

Sarasota, Florida

December 10 to 13, 1978

The meeting began with registration and an informal social gathering on Sunday, December 10, 1978. Drs. G. T. Bryan and O. Yoshida welcomed guests and visitors. The list of invited participants and observers follows this conference report. Observers were encouraged to participate during all open discussion periods of free time.

The opening session on December 11, 1978, began with a description of the organization and purposes of the Joint U.S.-Japan Cooperative Cancer Research Program. The purposes and goals of the present meeting are: (1) to discuss and demonstrate knowledge and concepts concerning clinical evaluation and multimodal therapeutic approaches to bladder cancer; (2) to share concepts and approaches involved in cooperative clinical trials in bladder cancer; and (3) to seek opportunities for joint collaborative clinical trials to be developed in the future. The participants had been invited to submit an abbreviated abstract of the contents of their assigned topics. Most were kind enough to prepare such abstracts. Following each block of presentations, discussion was comprehensive and vigorous. These discussions involved the full time allotted and continued through free periods and mealtimes.

Two highlights of the meeting are deserving of special commendation. Dr. Sachio Mochizuki reported on the use of radiotherapy for bladder cancer in Japan. He clearly demonstrated the use of intraoperative irradiation of small solitary bladder tumors, exposed by cystotomy, to a high energy electron beam therapy. The U.S. urologists and radiotherapists expressed enthusiastic interest in this approach. It is likely that this might serve as a focus for cooperative studies. The second major contribution involved the presentation of the design and conduct of clinical trials and collaborative studies. These reports largely dealt with the five-year experience of the U.S. National Bladder Cancer Project Collaborative Group A activities. Mr. Arthur Hilgar described the numerous considerations to be confronted in planning and organizing the collaborative clinical studies. This was followed by comments by Collaborative Group A participants of the roles of the urologist, radiotherapist, chemotherapist, pathologist, and statistician in such a complex program. Much interest was expressed in this portion of the seminar.

The meeting enjoyed the involvement and participation of each member of the delegations. The participant selection was excellent, and each counterpart member found a scientific colleague to interact with. Members of both delegations expressed interest in seeking new avenues to develop mutually shared clinical trials and to continue scientific exchanges in the future. It is clear that ways to facilitate such continued interactions must be developed.

The Japanese participants as well as the U.S. hosts continued to interact during the period December 13 to 15, 1978, while attending the National Bladder Cancer Project Investigators' Workshop. More than 300 individuals attended and participated in this meeting. Dr. O. Yoshida very kindly presented aspects of clinical bladder cancer research activities in Japan at a principal session of the meeting.

These meetings were excellent and the purposes described were met. Ample time was provided for exchange of ideas, and preliminary steps were taken toward continued interactions.

Finally, Professors Yoshida and Bryan wish to thank their advisors for providing the strength and direction to carry out these activities. The advisors from Japan are Dr. N. Ito and Dr. M. Okada. From the United States, the advisors are Drs. G.H. Friedell and C.M. King. It is appropriate that they should share in any successes; we accept responsibility for any shortcomings. The Japan Society for the Promotion of Science and the U.S. National Cancer Institute have been steadfast in their support and encouragement of this program and that support is gratefully acknowledged.

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CYTOLOGY
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Program Coordinators:
Dr. Kiyoji Kimura
Dr. Chester J. Herman

CYTOLOGY PROGRAM AREA REPORT

September 1977 to October 1978

Summary of Activities

Activities in this program area during the past year focussed on scientist exchanges.

EXCHANGE OF SCIENTISTS

The exchange of scientists continues to be one of the most productive activities of the Cytology Program Area. With the rapid development and application of new techniques in this field, scientists from both the United States and Japan benefit markedly from these visits.

During this reporting period, several exchanges took place:

1. Dr. Iwao Nishiya, Hokkaido University, Sapporo, visited the Laboratory of Pathology, NCI, October 1977 to August 1978.

   Sponsor: Dr. Chester Herman

   Subject: Cytochemical probes of chromatin structure and their application to hormonal effects on tumor cells.

2. Dr. Chester Herman, Laboratory of Pathology, NCI, visited the National Cancer Center, Tokyo, May 1978 to November 1978.

   Sponsors: Dr. Kiyoji Kimura and Dr. Yoshio Uei

   Subject: New clinical applications of quantitative cytology.

Five-Year Summary Report

During the first five years of the U.S.-Japan Cooperative Cancer Research Program, the initial objective of the Cytology Program Area has been achieved: The scientists of both countries have acquired a thorough working knowledge of the objectives, design, and in-service operation of each others' quantitative cytologic techniques.

Beyond this initial objective, the impact of this exchange of meetings and individual scientists has been tremendous. As a result of this program, there has been a surge of interest in flow analysis and sorting systems in Japan, with over two dozen groups now applying these techniques to a wide variety of basic and clinical research problems. Similarly, in response to the stimulus provided by the U.S.-Japan Cooperative Cancer Research Program, a renewed interest in the development and application of static slide-based image processing systems has arisen in the United States. Several new groups have been organized under the U.S. Cytology Automation Program to pursue the best in modern design and application of these techniques.

In addition to these major areas, extensive collaborative research between Japanese and American scientists has resulted in markedly improved specimen collection and preparation techniques in gynecologic cytology automation. Other new techniques such as indexed cell sorting have been explored by collaborative efforts.

Future Objectives

In Japan and the United States, quantitative cytology is a rapidly growing field, analogous to electron microscopy 25 to 30 years ago. Applications of quantitative cytologic techniques are being vigorously pursued in many areas of basic cell biology and applied oncology including: screening of cytology specimens for cancer cells; design and development of chemotherapeutic and radiotherapeutic protocols in model tumor systems and subsequent evaluation of these protocols in clinical specimens; basic research on macromolecules, cytoskeleton, and surface structure of malignant cells; and response of the immune system to tumors and their eradication.

With the restructuring of the U.S.-Japan Cooperative Cancer Research Program, involvement in essentially all of the areas of major interest by Japanese and U.S. scientists utilizing quantitative cytologic techniques should be sought.

Since quantitative cytologic methods are still in the phase of rapid development and application in a number of different biologic areas, there is a great need for continued contact at an intensive level among U.S. and Japanese scientists working with these techniques. For this purpose, the exchange of scientists has been demonstrably productive during the first five years of the Program and should be vigorously encouraged.

In addition, regular meetings of scientists working in this field are of great value. In the past, the regular conferences organized by the Engineering Foundation/Society for Analytic Cytology have represented the most current and complete worldwide exchange of methodology and applications in this area. Bilateral meetings of Japanese and U.S. scientists in conjunction with these conferences would be exceptionally cost-effective in stimulating expanded U.S.-Japan cooperation and collaboration in quantitative cytology.

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HIGH LET RADIOTHERAPY PROGRAM AREA REPORT

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High LET Radiation Therapy Workshop (Pennsylvania)

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Program Coordinators:
Dr. Akira Tsuya
Dr. Glenn E. Sheline

HIGH LET RADIOTHERAPY PROGRAM AREA REPORT

September 1977 to October 1978

Summary of Activities and Accomplishments

Activities during this reporting period included Meetings, Seminars, and Conferences; and the Exchange of Scientists.

MEETINGS, SEMINARS, AND CONFERENCES

A two-day symposium, the "High LET Radiation Therapy Workshop," was held on June 19 and 20, 1978, in Philadelphia, Pennsylvania. It was preceded by a business meeting on June 18. The symposium consisted of five sessions aimed at reviewing the present status of work in Japan and the United States with a total of 31 papers presented and discussed. The first session dealt with fast neutron radiobiology and radiotherapy with emphasis on clinical studies. The second session included three papers on radiobiology of charged particles, three on clinical trials with particulate radiations, and two on the status of high energy accelerator projects in Japan. The third session was on treatment planning with emphasis on the special problems of tissue inhomogeneity, compensating and field flattening filters, etc., related to treatment with charged particles. The fourth session concerned high dose rate brachytherapy and intraoperative therapy. It consisted of six papers in which clinical experiences in Japan and the U.S. with these forms of therapy were reviewed. The last session contained seven papers on hypoxic cell sensitizers and hyperthermia. Both radiobiologic and clinical studies were included (a listing of the papers presented at this workshop follows this report). The program concluded with a lively discussion on problems of conducting randomized clinical studies in the U.S. and Japan. It was evident that many fundamental scientific, cultural, and ethical problems are involved. This area needs further discussion.

Ten Japanese, twelve Americans, and one Canadian presented papers and/or formally participated in the symposium. Approximately 30 other Americans also attended and participated in the discussions; they were mostly representatives from various high LET projects currently active in the U.S.

In keeping with precedent set at previous meetings, this was a hard working symposium with high quality papers and free and lively discussion.

Another workshop was held in the period under consideration (September 29 and 30, 1977, Tokyo). The Summary Report is contained in the second two-year Progress Report for 1976 and 1977.

EXCHANGE OF SCIENTISTS

During this reporting period, two Japanese and four U.S. scientists participated in the exchange program.

Mitsuyuki Abe, M.D., Professor, Department of Radiology, Kyoto University Medical School, Kyoto, Japan, visited particle radiotherapy facilities in the U.S., participated in the Philadelphia symposium, and gave several lectures on intraoperative radiotherapy. His visits included the University of California at Berkeley (Dr. Cornelius Tobias), University of California at San Francisco (Drs. Theodore Phillips and Glenn Sheline), Los Alamos (Dr. Morton Kligerman), Howard University (Dr. Ulrich Henschke), the National Cancer Institute (Dr. Eli Glatstein), and the Massachusetts General Hospital (Dr. Herman Suit).

The second Japanese exchange scientist was Koichi Kaneta, M.D., Assistant Chief of the Division of Radiotherapy, Cancer Institute Hospital, Tokyo, Japan. Dr. Kaneta was chiefly concerned with Californium-252 brachytherapy, including the U.S. Radiation Therapy Oncology Group clinical trials. Discussions were held at Jefferson Medical School (Dr. H. Gunter Seydel), Memorial Sloan-Kettering Cancer Center (Dr. Basil Hilaris), M.D. Anderson Hospital (Dr. L. Delclos), the University of California at San Francisco (Dr. Theodore Phillips); and Albert B. Chandler Medical Center, University of Kentucky (Dr. Y. Maruyama).

Peter R. Almond, Ph.D., Professor, Department of Physics, M.D. Anderson Hospital and Tumor Institute, Houston, lectured at four facilities in Japan. These included Tohoku University in Sendai; the Radiological Society in Kansai District at Osaka; Tokyo University; and the National Institute of Radiological Sciences (NIRS) in Chiba. He spoke on various aspects of fast neutron radiotherapy as experienced with the Texas A & M variable energy cyclotron. Dr. Almond also conducted physical dosimetry measurements at the Institute of Medical Sciences (IMS) in Tokyo (completing the physical dosimetry intercomparison studies).

Hermann A. Grunder, Ph.D., Professor of Physics, University of California, Berkeley, reviewed the status of medical accelerators in Japan and worked with the Neutron Study and Design Group at the Institute for Nuclear Science near Tokyo. He visited and gave lectures at KEK (Tsukuba City), the Institute for Nuclear Science (Tokyo), the Institute for Physical and Chemical Research (Tokyo), Tohoku University (Sendai), the Research Center for Nuclear Physics (Osaka University), the pion facility at Nihon University and NIRS at Chiba.

Theodore L. Phillips, M.D., Professor, Division of Radiation Oncology, University of California at San Francisco, visited and gave lectures at Tohoku University (Dr. Matsuzawa), Kyoto University (Dr. M. Abe), the regional Radiological Society meeting at Osaka, Tokyo University (Dr. Okada), and NIRS in Chiba (Dr. Umegaki). His primary interest was related to high LET radiobiology and radiotherapy but lectures and discussion included hypoxic cell sensitizers and intraoperative radiotherapy.

Herman D. Suit, M.D., Ph.D., Professor of Radiation Medicine, Massachusetts General Hospital, Boston, visited the Medical Center at Sapporo (Dr. Kikuchi), Kyoto University Medical Center (Dr. M. Abe), University of Tokyo Medical Center (Drs. Okada and Sakamoto), IMS in Tokyo (Dr. Ito), and NIRS in Chiba (Dr. Umegaki). Dr. Suit gave lectures on clinical studies with proton beams and participated in seminars on basic radiobiology.

Five-Year Summary Report

The initial High LET Radiotherapy Program goals were to review the status of high LET radiation physics, radiobiology, and clinical trials and then to promote use of high LET particle therapy in the two countries. The intent was to develop a common body of knowledge and mutually accepted dosimetry (both radiobiological and physical), and to extend this activity to controlled clinical trials. It was also intended that related subject areas would be added as interest dictated. The program began with a study of fast neutron beams (neutron studies were more advanced in both countries) and was then extended to other particle beams. Since the initial contact in the Spring of 1975, the program has developed precisely along these lines and has been imminently successful from the viewpoints of both countries.

Intercomparative physical and biological dosimetry studies have been completed for all fast neutron beams in clinical use in the U.S. and Japan. These have included detailed physical and radiobiological measurements on the various neutron beams. Common dosimetry and similar dose units form the basis for any exchange of information and for international confidence in work reported.

While the radiobiological and physical dosimetry studies were in progress, discussions on controlled clinical trials were carried out. Even though no bilaterally acceptable randomized trial has as yet been formulated, the discussions influenced and aided development of protocols in each country. With respect to possible common protocols, the first effort concerned carcinoma of the uterine cervix. However, due to differences in the manner in which brachytherapy is used in the two countries (low dose rate and long exposure time in the United States versus high dose rate and short application times in Japan), carcinoma of the cervix may not prove to be a good choice for a common protocol. Other disease sites for common studies are being investigated.

Simultaneous with discussions on neutrons, consideration has been given to other particles. This has provided a valuable exchange of information and promoted basic research in both countries. Particles under consideration include protons, negative pi-mesons, carbon, and neon. Questions of design and construction of appropriate dedicated medical sources for particle beams have been dealt with in detail. Electron linacs currently are favored at Stanford University (California) and in Japan. At Los Alamos, a proton linac is under development and may, in the near future, become the machine of choice. The program has aided and stimulated the design and construction of such equipment in both countries. Since the costs involved are high, mutual assistance is of great value.

During the last few years there has been great interest in hypoxic cell sensitizers. There is a possibility that these may be of value in conjunction with particle therapy, or even in obviating the need for particle therapy. For this reason, the last "high LET" workshop (Philadelphia, 1978) included a session on hypoxic cell radiosensitizers. This session reviewed the present status of work in Japan and in the U.S. and explored possible areas for cooperation. It was evident that much interest exists in both countries. Radiobiological studies with cell cultures and animal tumor systems and clinical Phase I and Phase II trials are underway. Evident areas for cooperation include exchange of information, exchange of sensitizer compounds, and, later, clinical trials.

The 1978 symposium also included a discussion of intraoperative radiotherapy, an area under active investigation in Japan and in one site in the U.S. (Howard University). Other U.S. institutions (e.g., Massachusetts General Hospital, Boston) are developing the necessary facilities. In addition to the many technical difficulties, a substantial outlay of resources is required for delivery of radiation therapy in a sterile operating room type environment. Thus, much may be gained from exchange of technical information. Ultimately, the efficacy of the method must be tested through clinical trials. Since the method is time-consuming and the number of patients with suitable lesions limited, meaningful clinical trials will require cooperation between multiple institutions.

Future activities include continuation of studies on the physics and biology of neutrons, development of clinical trials, design and development of medically dedicated sources for particle beams, biological and physical dosimetry intercomparison studies for particles other than neutrons as they become available for biological and clinical use, and cooperative studies with hypoxic cell radiosensitizers and intraoperative therapy. Given time and resources, there are no inherent difficulties foreseeable in the design and development of particle radiation sources or in the conduct of the biological and physical studies outlined. Differences in attitude may impose philosophical constraints on randomized clinical trials. This most important area requires careful attention. Either suitable areas for randomized trials should be found, or methodology should be developed to circumvent the need for randomization.

CONFERENCE REPORTS

HIGH LET RADIATION THERAPY WORKSHOP

Philadelphia, Pennsylvania

June 19 and 20, 1978

AGENDA

Co-Chairmen: **Akira Tsuya, M.D.**
Glenn E. Sheline, Ph.D., M.D.

Session I: **Fast Neutron Radiobiology and Radiotherapy**
(Convener: **Dr. T. L. Phillips**)

1. The Effect of Fast Neutrons on Chinese Hamster V79 Cultured Cells in Murine Epithelioma—**K. Sakamoto,** University of Tokyo
2. The Status of U.S. Clinical Neutron Studies—**L. Davis**
3. Results of Fast Neutron Therapy at NIRS—**S. Morita**
4. Fast Neutron Clinical Trial on Uterine Cervix Cancer at NIRS—**S. Morita**
5. U.S. Fast Neutron Clinical Trial for Cancer of the Cervix—**D. Hussey**
6. A Comparison of U.S. and Japanese Clinical Trials with Fast Neutrons for Carcinoma of the Cervix—**D. Hussey** and **T. Phillips**

Session II: **Proton and Charged Particle Radiobiology and Radiotherapy**
(Convener: **Dr. L. Davis**)

1. Radiobiology of 160-MeV Protons—**M. Urano**
2. Proton Therapy of Choroidal Melanoma with Discussion
—**Y. Umegaki** and **H. Suit**
3. Update of Radiobiology of Charged Particles—**T. Phillips**
4. Clinical Trials with Charged Particles—**J. Castro**
5. The Effect of Negative Pi-meson on Murine Epithelioma—**K. Sakamoto**
6. Clinical Trials with Pions—**M. Kligerman**
7. High Energy Accelerator Projects with Medical Program in Japan—**S. Fukumoto**
8. Project Plan of Pi-meson Therapy Facility at Nihon University—**O. Hara**

Session III: **Treatment Planning**
(Convener: **Dr. J. Castro**)

1. Improved Physical Dose Distribution from Fast Neutron Beams (Build-up, Depth Dose, Inhomogeneities, Modification of Dose Distribution, etc.)—**V. Otte**
2. Treatment Planning for Charged Particle Radiotherapy—**G. Chen**
3. Planning of Proton Therapy at NIRS—**Y. Umegaki**

Session IV: **High Dose Rate Brachytherapy and Intraoperative Therapy**
(Convener:**Dr. H. Suit**)

1. High Dose Rate Brachytherapy for Gynecologic Cancer, Methods and Results —**S. Morita**
2. Experiences in U.S. with High Dose Rate Brachytherapy—**J. Utley**
3. Experiences with Intraoperative Radiotherapy at the Kyoto University Hospital —**M. Abe**
4. Clinical Experiences of the Intraoperative Radiotherapy of Cancer of the Bladder and Digestive Tract—**Y. Umegaki**
5. Intraoperative Radiotherapy—**A. Goldson**
6. Is There a Place for Hypoxic Cell Sensitizers with Intraoperative or High Dose Rate Brachytherapy?—**T. Phillips**

Session V: **Hypoxic Cell Sensitizers and Radioprotectors**
(Convener: **Dr. E. J. Hall**)

1. Present State of Studies on Anoxic Sensitizers and Hyperthermia in Japan —**Y. Onoyama**
2. Experimental Animal Tumor Irradiation Using Hypoxic Sensitizer—**M. Abe**
3. Sensitizing Effect of Misonidazole on Spontaneous Mammary Carcinoma of C_3H Mice —**Y. Onoyama**
4. C. PARVUM Enhanced Thermal Response of Murine Tumors—**M. Urano**
5. Hypoxic Cell Radiosensitizers—**E. Hall**
6. Clinical Studies with Radiosensitizers—**R. Urtasun**
7. Clinical Studies with Radiosensitizers—**T. Phillips**
8. Discussion of Areas for Joint Studies—**H. Suit**

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LUNG CANCER
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CONFERENCE REPORT

Fourth Joint Seminar on Lung Cancer (Honolulu)

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Program Coordinators:
Dr. Yuichi Yamamura
Dr. Oleg Selawry

LUNG CANCER PROGRAM AREA REPORT

September 1977 to October 1978

Summary of Activities

During this reporting period, activities of the Lung Cancer Program Area were as follows:

MEETINGS, SEMINARS, AND CONFERENCES

The Fourth Joint Seminar on Lung Cancer was held in the East-West Center, Honolulu, Hawaii, on February 2 and 3, 1978, on the subject of Multidisciplinary Treatment of Lung Cancer. This conference was attended by seven American and six Japanese participants and included 15 presentations with six discussion periods covering progress in:

1. **Morphology.** Dr. Raymond Yesner, Chairman of the WHO Committee, and Dr. Yukio Shimosato, a member of the WHO Committee, presented the WHO Second Edition of *Morphology of Pulmonary Neoplasms*.
2. **Immunotherapy.** Dr. Yuichi Yamamura presented the newest advances in chemistry and clinical application of cell-wall skeletons; Dr. Kenneth Ramming presented current data on surgical adjuvant intratumorous injection of BCG; and Dr. Ramming of the U.S. and Dr. Mitsuo Ohta of Japan presented the present status of immunotherapy in the United States.
3. **Multidisciplinary Treatment of Small Cell Carcinoma.** Dr. Shoji Hattori presented multidisciplinary treatment in Japan, including surgery; Dr. Ralph Johnson presented experiences with aggressive radiotherapy and chemotherapy; and Dr. Lawrence Broder presented treatment with non-cross resistant drug combinations.
4. **Multidisciplinary Treatment of Non-small Cell Cancer.** Summaries for Japan were presented by Dr. Shoji Hattori and for the U.S. by Dr. Oleg Selawry, stressing the consistent 60 percent response rates for chemotherapy of adenocarcinoma.
5. **Adjuvant Surgery.** Drs. Clifton Mountain and Keiichi Suemasu presented summaries.
6. **Cell Kinetics and Marker Substances.** The impact of cell kinetics and marker substances on planning and monitoring of therapeutic studies were presented by Drs. Marc Strauss and Lawrence Broder.

The presentations at this seminar reflected considerable mutual progress in all areas of the Lung Cancer Program Area. The agenda of this meeting follows this report.

EXCHANGE OF SCIENTISTS

Two American scientists, Dr. Clifton Mountain and Dr. Oleg Selawry, made highly rewarding visits to Japan during this reporting period. From June 26 to July 7, they visited the National Cancer Center Hospital (Dr. Ishikawa); the Tokyo Medical College (Dr. Hayata); Aichi Medical Center, Nagoya (Dr. Nishimura); Osaka Medical Center (Dr. Yamamura); the Center for Adult Diseases in Osaka (Dr. Hattori); and the Kyushu Cancer Center in Fukuoka (Dr. Ohta). They learned about progress in fiberoptic bronchoscopy from Dr. Ikeda at the Cancer Center Hospital and from Dr. Oho at the Tokyo Medical College; new needles for transthoracic biopsy (Dr. Oho); chemistry and experimental data on cell-wall skeletons of various origins (Dr. Yamamura and co-workers); and clinical experience with these cell-wall skeletons (Drs. Hayata, Yamamura, Hattori, Ohta, and co-workers).

During their very stimulating meetings with these Japanese scientists, Dr. Mountain had the opportunity to present his own data on surgical staging and surgical adjuvant treatment, and Dr. Selawry presented data on chemotherapy.

Two Japanese scientists visited and studied in the United States as part of the exchange program of the Lung Cancer Program Area. Dr. Nagahiro Saijo, of the National Cancer Center Hospital in Tokyo, studied at the M.D. Anderson Hospital in Houston, Texas; visited the Comprehensive Cancer Center for the State of Florida (Miami) and the National Cancer Institute (NCI) in Bethesda, Maryland; and participated in the Annual Meeting of ASCO/AACR in Washington, D.C. These activities took place from March to July 1978.

Dr. Ryuhei Tateishi, of the Department of Pathology, Center for Adult Diseases (Osaka), visited the United States from June 28 to July 29, 1978. His activities included visits to the New Haven Veterans Hospital; the Memorial Sloan-Kettering Cancer Center; the Washington, D.C., Veterans Administration Hospital; and the Mayo Clinic.

FIVE-YEAR SUMMARY REPORT

The following activities summarize the accomplishments of the Lung Cancer Program Area over the past five years:

1. **Staging.** Drs. Mountain and Ishikawa advanced fully compatible and very similar staging systems for bronchogenic carcinoma. These staging systems are generally and widely accepted as the official staging systems in both countries.

2. **Morphology.** Drs. Yesner, Shimosato, Melamed, Matthews, and Hattori reached full agreement on morphologic classification by cell type and ascertained congruence of interpretation by mutual slide reviews. Dr. Selawry had the opportunity to recommend representatives of both countries to the morphology committee of WHO (Dr. Sobin) for an update of the WHO Classification of Lung Cancer. Thus, Dr. Yesner was invited as chairman of the WHO Committee and Dr. Shimosato as Committee Member, leading to the integration of their mutual work into the updated WHO publication *Morphology of Pulmonary Neoplasms* (Second Edition). This classification has found worldwide acceptance.

3. **Early Diagnosis.** (Drs. Frost, Sanderson, Fontana, Beattie, Ikeda, and Oho). The Japanese investigators developed fiberoptic bronchoscopy and trained U.S. investigators in the use of these instruments for early diagnosis of cytology-positive, chestfilm negative cancer. The U.S. investigators, in turn, tested the new methodology in a major NCI-supported field trial (Dr. Berlin) and shared their results with their colleagues in Japan.

4. **Therapy with Emphasis on Multidisciplinary Treatment.** (Drs. Selawry and Yamamura). U.S. investigators advanced the methodology of comparative clinical trials and the logic of drug development (Phase I to III Trials), now increasingly accepted in Japan. Japanese investigators defined the chemical structures of cell-wall skeletons and modified them, leading to reproducible and improved immunotherapeutic agents. Both countries contributed greatly to the development of antineoplastic drugs (discussed elsewhere). Exchange contributed to impressive initial results in adjuvant immunotherapy and to substantial increases in response rate (including complete tumor regression in 40 to 60 percent of small-cell carcinoma) and longevity, notably in patients with small-cell and adenocarcinoma.

5. The U.S. Co-Chairman, Dr. Selawry, was elected the first non-Japanese honorary member of the Japan Lung Cancer Society.
6. Dr. Yamamura is a frequent participant in conferences and workshops in the U.S. on immunotherapy of lung cancer. Cell-wall skeletons from BCG and *Nocardia rubra* find increasing interest in laboratories and clinical studies in the United States.

Future Problems and Developments

Efforts over the last five years were mainly directed at better cure rates and more effective palliation of lung cancer. On the basis of this work, we are now prepared to extend our joint program toward prevention.

Agreement on diagnosis by cell type will permit the mapping of lung cancer incidence by cell type in order to focus on etiologic factors, which commonly express themselves in a relative increase of squamous and small-cell carcinoma, respectively. This might aid in cancer prevention by decreased exposure to carcinogens and co-carcinogens.

An increasing number of anticarcinogenic principles are successfully advanced against carcinogen-incuded respiratory cancer in animals. These include among others, analogues of retinoic acid (Bollag, Nettesheim, Sporn) and cell-wall skeletons of BCG and *Norcardia rubra*. Phase I studies and preliminary Phase II data on refined acid analogues are in progress.

Thus, controlled clinical trials in persons at high risk are in sight. If successful, they might represent the single most successful application of currently available methodology toward a decrease of lung cancer incidence and mortality.

The Fifth Joint Meeting of the Lung Cancer Program Area held in Miami, Florida, in February 1979, reflects this transition, focusing on squamous cell carcinoma and moving from treatment to chemoprevention and immunoprevention.

CONFERENCE REPORTS

FOURTH JOINT SEMINAR ON LUNG CANCER

East-West Center
Honolulu, Hawaii

February 2 and 3, 1978

AGENDA

Thursday, February 2

9:00 a.m. Introductory Remarks—**Dr. Selawry** and **Dr. Yamamura**

9:10 a.m. **Session I:**
Progress in Morphology: The Updated WHO Classification of Lung Cancer, With Special Reference to the Morphologic Subtypes of Small-Cell and Large-Cell Carcinoma

9:30 a.m. **Dr. Yesner**—Chairman, WHO Committee for the Morphologic Classification of Lung Cancer

9:50 a.m. **Dr. Shimosato**—Member, WHO Committee for the Morphologic Classification of Lung Cancer

10:10 a.m. Discussion

10:25 a.m. COFFEE BREAK

10:40 a.m. **Session II:**
Advances in Immunotherapy of Lung Cancer
Moderators: **Dr. Yesner** and **Dr. Hayata**

Dr. Yamamura—Immunotherapy of Carcinomatous Pleuritis with BCG Cell-Wall Skeleton

11:10 a.m. **Dr. Ramming**—The Present State of Immunotherapy of Lung Cancer in the U.S.A. Intratumoral Injection of Immunostimulants

11:30 a.m. **Dr. Ohta**—Immunotherapy and Surgery of Lung Cancer

11:50 a.m. Discussion

12:05 p.m. LUNCH

Thursday, February 2 (continued)

Session III:
Progress in the Treatment of Small Cell Carcinoma

Moderators: **Dr. Suemasu** and **Dr. Strauss**

2:15 p.m. **Dr. Broder**—Non-Cross Resistant Drug Combinations Rationale and Current Experience

2:35 p.m. **Dr. Hattori**—Multidisciplinary Treatment

2:55 p.m. **Dr. Ralph Johnson**—Considerations for Optimal Combination of Chemotherapy and Radiotherapy

3:15 p.m. Discussion

3:30 p.m. COFFEE BREAK

Session VI:
Treatment of Non-Small Cell Lung Cancer

Moderators: **Dr. Broder** and **Dr. Hattori**

3:45 p.m. **Dr. Hayata**—Multidisciplinary Treatment

4:05 p.m. **Dr. Selawry**—Progress in Chemotherapy

4:25 p.m. Discussion

Evening: Reception for the Japanese Delegation

Friday, February 3

Session V:
Indications for Surgery in Advanced Lung Cancer

Moderators: **Dr. Ohta** and **Dr. Ramming**

9:00 a.m. **Dr. Mountain**

9:20 a.m. **Dr. Suemasu**

9:40 a.m. Discussion

9:55 a.m. COFFEE BREAK

Session VI:
Cell Kinetics and Marker Substances. Their Role for Planning and Monitoring of Therapeutic Studies

Moderators: **Dr. Yamamura** and **Dr. Ralph Johnson**

10:10 a.m. **Dr. Strauss**—Clinical Trials based on Cell Kinetics of Lung Cancer

10:30 a.m. **Dr. Broder**—Marker Substances in Lung Cancer: Incidence and Correlation with Clinical Course

10:50 a.m. Discussion

Session VII:
Business Meeting—General Discussion and Future Plans

Moderators: **Dr. Selawry** and **Dr. Yamamura**

12:00 noon Adjourn

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Program Coordinators:
Dr. Haruo Sato
Dr. Philip G. Stansly

METASTASIS PROGRAM AREA REPORT

September 1977 to October 1978

Summary Report

The past year has seen an increased interest in metastasis research. A beginning has been made in the joint effort to study metastasis under the U.S.-Japan Cooperative Cancer Research Program, and interest among investigators has gained momentum. Investigations must be accomplished to understand the location of tumor cells, transport lodgment of micrometastatic cells, vascularization of cells and tissue, and the formation of metastatic foci.

MEETINGS, SEMINARS, AND CONFERENCES

A workshop on "Experimental Approaches to the Therapy of Micrometastasis" was held in Nara, Japan, from October 26 to 28, 1978. The extremely informative and stimulating discussions included such topics as: immunologic host factors; properties of metastatic cells, including cell membrane, and the differences in the enzymes in normal and tumor cells; the effect of glucose on potentiating drugs, delivery of antitumor drugs to tumor cells; and studies of models. The metastatic process is very important in several types of cancer (such as lung cancer) and until the mechanisms of metastasis can be well understood and properly treated, it was generally concluded at this meeting that cancer cannot be conquered. Brief reports were presented on the possible role of protease inhibitors in the therapy of micrometastasis. The mechanism of action and joint study on the use of a model system to study the role of protease inhibitors were also discussed.

EXCHANGE OF SCIENTISTS

Dr. Saburo Sone, from Dr. Eiro Tsubura's laboratory at Tokushima University, will join Dr. Fidler as a Research Fellow to collaborate on studies of the lympohcyte-macrophage system for the therapy of micrometastasis.

Five-Year Summary Report

The first five years of collaboration between Japan and the United States produced significant achievements through the scientific interaction of Japanese and American investigators. A summary of the activities during this five-year period is highlighted below.

MEETINGS, SEMINARS, AND CONFERENCES

At the invitation of the U.S. coordinator, a small contingent of American and Japanese scientists met in Bethesda, Maryland, on March 7, 1975, to plan future activities for the Metastasis Program Area. This meeting resulted initially in the participation of several Japanese investigators in a workshop/symposium on "Fundamental Aspects of Metastasis" at Roswell Park Memorial Institute in July 1975. The proceedings of this symposium were published in 1976 (*Fundamental Aspects of Metastasis*, edited by L. Weiss, Elsevier Publishing Company, New York).

In May 1976, eight Japanese and ten American scientists participated in the "Workshop on Metastasis" sponsored by the U.S.-Japan Cooperative Cancer Research Program and held in Kona, Hawaii. The results of this workshop were published in GANN Monograph on Cancer Research (No. 20): *Cancer Metastasis: Approaches to the Mechanism, Prevention and Treatment* (edited by P.G. Stansly and H. Sato, University Park Press, Baltimore, 1977).

The Memorial Sloan-Kettering Cancer Institute and the National Cancer Institute (NCI) later collaborated in a conference and workshop on metastasis held in New York in November 1976. The U.S.-Japan Cooperative Cancer Research Program was included in this effort and the Japanese investigators were supported with funds provided by the NCI. This conference was subsequently also published in *Progress in Cancer Research and Therapy*, Volume 5, "Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy" (edited by S.B. Day, W.P. Laird, P.G. Stansly, S. Garrattini, and M.G. Lewis, Raven Press, New York, 1977).

Exchange of Scientists

Three Japanese scientists spent varying amounts of time in collaborative research in U.S. laboratories under the auspices of the U.S.-Japan Program as follows:

- During February and March 1975, Dr. Maroh Suzuki, Tohoku University, collaborated with Dr. Benjamin Zweifach at the University of California at San Diego.
- Dr. Toshio Takahashi, Akita University, visited with Dr. Bernard Fisher, University of Pittsburgh, November 1975 through January 1976.
- Dr. Noritaka Kimura, Kyushu University, collaborated with Dr. Joseph Leighton, Medical College of Pennsylvania, for seven months, from September 1976 to March 1977.

Two American investigators, Dr. Isaiah J. Fidler, Frederick Cancer Research Center, and Dr. George Poste, Roswell Park Memorial Institute, spent two weeks lecturing at eight Japanese medical research centers from May 29 to June 15, 1977. This activity was sponsored by the exchange scientists program of the U.S.-Japan Cooperative Cancer Research Program.

GENERAL COMMENTS

There is no doubt that the U.S.-Japan Cooperative Cancer Research Program serves a useful function in encouraging scientific interaction between our two countries. Japanese and American investigators, who otherwise might not have encountered each other, have grown to appreciate each others skills and perceptions and, as a result, are in a better position to collaborate in areas of mutual interest, an activity which is now taking place.

Despite the limited progress in understanding and controlling the metastatic process, it is hoped that this area of the U.S.-Japan Program will maintain visibility. It is a most important aspect of clinical cancer research and needs special stimulation and support precisely because it is a poorly understood process and a frustrating area of research. It can easily fall into a state of neglect as investigators become discouraged and seek greener pastures.

Dr. Isaiah J. Fidler, of the Frederick Cancer Research Center, was recommended to represent American interest and to help sustain the momentum in metastasis research that has already been achieved in the U.S.-Japan Cooperative Cancer Research Program.

CONFERENCE REPORTS

WORKSHOP ON EXPERIMENTAL APPROACHES TO THE THERAPY OF MICROMETASTASES

Nara, Japan

October 26 to 28, 1978

AGENDA

Coordinators: **Dr. Philip G. Stansly, National Cancer Institute, Bethesda**
Dr. Haruo Sato, Tohoku University, Sendai

Thursday, October 26

9:00 a.m.	Welcoming Remarks	**H. Sato**
9:10 a.m.	Plan of Workshop	**P. Stansly**

Chairman: **P. Stansly**

9:20 a.m.	Introduction to Biology of Metastasis—Individuality in Malignant Tumor	**H. Sato**
9:50 a.m.	Discussion	
10:00 a.m.	COFFEE	

Session 1: Models for Experimental Metastasis

Chairmen: **M. Kripke** and **S. Tsukagoshi**

11:00 a.m.	Experimental Models for the Study of Metastasis	**G. Poste**
11:20 a.m.	Discussion	
11:30 a.m.	U.V. Carcinogenesis	**M. Kripke**
11:50 a.m.	Discussion	

Session 2: Host Factors in Metastasis

Chairmen: **L. Peters** and **K. Tanaka**

2:00 p.m.	Host Factors in Inhibition of Metastasis in Lewis Lung Tumor	**E. Tsubura**

Thursday, October 26 (continued)

2:20 p.m.	Discussion	
2:30 p.m.	Immunologic Factors in UV Carcinogenesis	**M. Kripke**
2:50 p.m.	Discussion	
3:00 p.m.	COFFEE	

Session 3: Tumor Factors in Metastasis

Chairmen: **H. Sato** and **J. Killion**

3:30 p.m.	Fate of Tumor Cells Arrested in the Lung of Nude Mice	**K. Tanaka**
3:50 p.m.	Discussion	
4:00 p.m.	Heterogeneity of Metastatic Tumor Cells	**I. Fidler**
4:20 p.m.	Discussion	
4:30 p.m.	Characteristic Blood Circulation in Tumor Tissue	**M. Suzuki**
4:50 p.m.	Discussion	
5:00 p.m.	Some Biologic Characteristics of Clinical Lymph Node Metastasis	**E. Sugarbaker**
5:20 p.m.	Discussion	

Friday, October 27

Session 3: Therapy by Manipulation of the Host

Immunotherapy

Chairmen: **I. Fidler** and **H. Kobayashi**

9:00 a.m.	Prevention of Metastasis with Cell Wall Skeletons of BCG and *Nocardia rubra*	**T. Ogura**
9:20 a.m.	Discussion	
9:30 a.m.	Immunogenic Properties of Tumor Cell Vaccines	**J. Killion**
9:50 a.m.	Discussion	
10:00 a.m.	COFFEE	

Friday, October 27 (continued)

10:30 a.m.	Enhanced Metastasis of Rat Tumor Cells after Cryosurgery	**H. Kobayashi**
10:50 a.m.	Discussion	
11:00 a.m.	Effect of Progressive Tumor Growth and Tumor Extracts on Macrophage Proliferation and Metastasis in a Murine Model	**E. Sugarbaker**
11:20 a.m.	Discussion	

Hyperthermia

Chairmen: **T. Baba** and **L. Peters**

1:30 p.m.	The Influence of Hyperthermia on Tumor Metastasis	**L. Peters**
1:50 p.m.	Discussion	
2:00 p.m.	Selective Intratumoral Potentiation of Anticancer Drug Effect by Glucose Treatment of the Host: Two Experimental Evidences	**T. Baba**
2:20 p.m.	Discussion	
3:00 p.m.	COFFEE	

Session 4: Regression of Micrometastasis

Chairmen: **L. Liotta** and **T. Matsushima**

3:30 p.m.	Regression of Tumor Metastasis by Viral Xenogenization	**H. Kobayashi**
3:50 p.m.	Discussion	
4:00 p.m.	Monitoring the Death Rate of Artificial Murine Pulmonary Micrometastasis	**L. Liotta**
4:20 p.m.	Discussion	

Session 5: Chemotherapy of Micrometastasis

Chairmen: **H. Watanabe** and **E. Sugarbaker**

4:30 p.m.	Suppression of Metastasis by Protease Inhibitors of Microbial Origin	**T. Matsushima**
4:50 p.m.	Discussion	

Friday, October 27 (continued)

5:00 p.m.	Experimental and Clinical Studies of the Treatment with Local Application of Solid-form Anti-cancer Agent (Bleomycin) as an Adjuvant Lymph Node Dissection	**H. Watanabe**
5:20 p.m.	Discussion	
5:30 p.m.	Mechanism of Enhancement of Tumor Transplantability by Irradiation and Cytotoxic Drugs	**L. Peters**
5:50 p.m.	Discussion	

Saturday, October 28

Session 6: Delivery of Drugs

Chairmen: **G. Poste** and **T. Takahashi**

9:30 a.m.	Delivery of Antitumor Drugs to Experimental Lymph Node Metastasis	**S. Tsukagoshi**
9:50 a.m.	Discussion	
10:00 a.m.	New Approaches to Drug Delivery in Cancer Chemotherapy	**G. Poste**
10:20 a.m.	Discussion	
10:30 a.m.	COFFEE	
11:00 a.m.	Enhancement of Chemotherapeutic Effect on Lymph Node Metastasis by Anticancer Agents in Fat Emulsion	**T. Takahashi**
11:20 a.m.	Discussion	
1:30 p.m.	Participants Separate into Groups to Work out Details of Collaborative Protocols	
2:00 p.m.	Working Groups Report to Participants	
2:30 p.m.	Consideration of Future Efforts of U.S.-Japan Program on Micrometastasis—**Dr. Stansly, Dr. Sato,** and **Conferees**	
3:00 p.m.	Adjourn	

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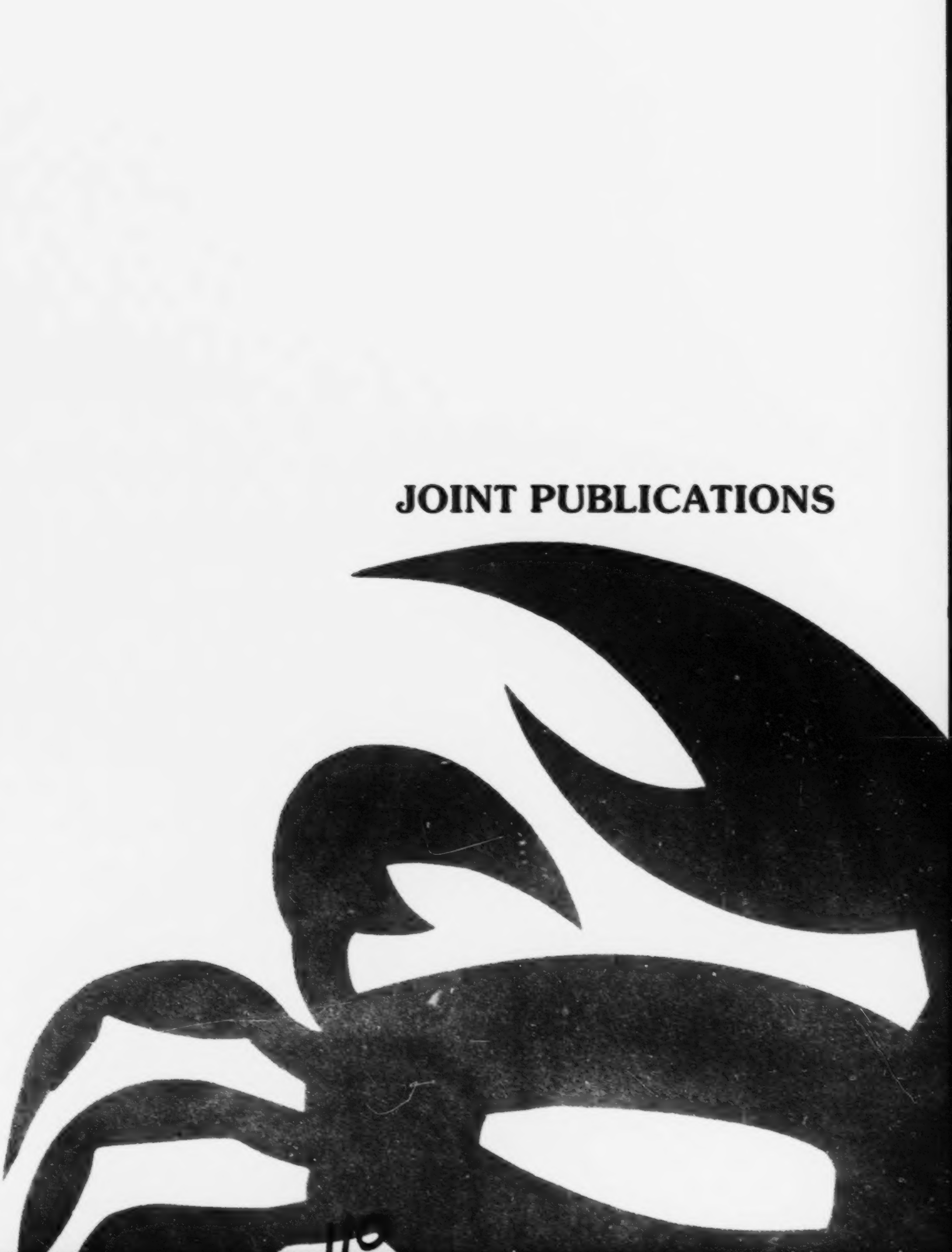

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MINUTES OF THE JOINT
STEERING COMMITTEE MEETING

Co-Chairmen:
Dr. Haruo Suqano
Dr. Guy R. Newell

MINUTES OF THE JOINT STEERING COMMITTEE MEETING

Tokyo, Japan

June 2 and 3, 1978

The meeting was called to order by Dr. Haruo Sugano, Co-Chairman of the Joint Steering Committee. He welcomed the U.S. Delegation: Dr. Guy R. Newell, Co-Chairman, Drs. William Terry, Stephen K. Carter, Robert W. Miller (substituting for Dr. I. Bernard Weinstein), Chester J. Herman (observer), and Robert R. Omata.

He then introduced the Japanese delegation: Mr. Isao Amagi, Director-General, JSPS; Mr. Saburo Kasagi, Executive Director, JSPS; Drs. Yoshio Sakurai, Yuichi Yamamura, Takashi Sugimura, Yoji Ikawa (observer), Mr. Kichimasa Soda, Mr. Nagahide Onozawa, and Mr. Iwao Abe, JSPS.

Dr. Sugano presented a brief summary of the first meeting of the Joint Steering Committee which was held at the National Cancer Institute (NCI), Bethesda, Maryland, in August 1977.

He then stated the purposes of this second meeting: (1) to review the draft of the Second Progress Report (1976-77) of the U.S.-Japan Cooperative Cancer Research Program; and (2) to discuss the proposal to restructure the Program for the second five-year period.

Dr. Newell thanked the Japanese Delegation for their kind remarks and stated that it is always a treat to visit Japan. He stated that he was delighted to be able to discuss and plan the strategy for a stronger and more flexible Program. He then introduced the U.S. Delegation.

Dr. Newell expressed the appreciation of the Joint Steering Committee to the Drafting Subcommittee for their efforts in compiling the Second Progress Report. The Subcommittee members were: Drs. Yoji Ikawa, Takeshi Hirayama, Chester J. Herman, Glenn E. Sheline, Robert R. Omata, and Mrs. Yuko K. Furukawa. He especially recognized the work of Mrs. Furukawa during the time she was with the Program for her unstinting devotion and talent and wished her well in her new duties.

He thanked the JSPS staff for their arrangements in scheduling the meeting in Tokyo for the convenience of the U.S. Delegation.

Mr. Amagi extended the welcome of the JSPS and the Japanese Delegation to the U.S. Delegation. He expressed appreciation, on behalf of the JSPS, for the progress and achievements made by the U.S.-Japan Cooperative Cancer Research Program. He then thanked all of the participants for their efforts and contributions toward attaining the objectives of the Program.

He stated that the first five years of the Program had a great impact in both countries through the media of seminars, workshops, exchange of scientists, exchange of resources and materials, and the multidisciplinary approach to cancer research engendered by the Program.

He stated that the JSPS was greatly in favor of extending the Program into the second five-year period and looked forward to the outcome of the deliberations of this meeting to propose a program plan in order to provide more new information on cancer to the scientific and lay communities. Recent progress and developments in science have given rise to new problems in public opinion; however, new knowledge must advance for the benefit of mankind. He stated that he hopes that target and priority areas will be set for the next five years and that the restructuring of the Program will provide greater responsibility to the Steering Committee and the Program Coordinators. He stated that he will do his best to obtain substantial funds to support the Program. In closing, he wished the Joint Steering Committee great success.

Dr. Sugano asked for a motion to approve the agenda. The motion for acceptance was made and unanimously approved. It was moved and approved that the meeting would start at 9:30 a.m. on Saturday June 3, 1978.

Dr. Sugano asked for any questions regarding the final draft of the Second Progress Report. He asked Dr. Omata to provide a brief background of the formation of the Drafting Subcommittee and the work done by the Subcommittee in March 1978.

Dr. Ikawa stated that the Minutes of the First Joint Steering Committee were included in the Progress Report and that the Memorandum from the Drafting Subcommittee was sent to the Joint Steering Committee. This was done since there was some concern expressed by the members during the drafting of the Second Progress Report that these documents be included.

There was considerable discussion concerning the different technical areas that should be included under each of the new program areas. The general consensus was that there should be flexibility to allow for the inclusion of new research areas for support under this cooperative program, particularly in those areas which are not currently included.

It was suggested by Dr. Herman that each program area should have a "working group" to advise the Program Area Coordinators. The Program Area Coordinators will have greater responsibility to seek out and/or provide support for new research interests and also to obtain maximum benefits or accomplishments from future exchange scientists.

Dr. Terry stated that he would like to see one meeting per year of the Joint Steering Committee and one large conference to be held biennially. The large conferences would have lower priority than the smaller working seminars, meetings, and workshops, particularly when funds are limited.

Mr. Soda stated that the Joint Annual Review Meetings should be abolished. The Committee generally agreed.

The Interdisciplinary Program Area Coordinators will be in the position of convening the large biennial conferences on subjects of current interest.

It was agreed that the Joint Steering Committee Meetings should be small and the subject of the biennial meetings or conferences should be decided by the Joint Steering Committee.

Dr. Sugimura presented a possibility that a topic, such as Prevention of Cancer, would be an appropriate multidisciplinary subject area which would provide a large forum for experts as well as give visibility and publicity to the U.S.-Japan Cooperative Cancer Research Program. Dr. Newell stated that the conference should be semi-open; participants should continue to be invited, and the locale should be accessible to the scientific community in both countries.

It was agreed that the October 31 and November 1, 1978, Annual Joint Meeting will be held in Japan in the same format as in previous years. At that time, the new proposed plan for the Second Five-Year Program will be announced and suggestions from the Joint Scientific Group will be solicited for further program planning.

One of the main reasons behind the restructuring of the Program will be to permit new people to participate and new ideas to be explored by supporting seminars and workshops.

It was agreed that the current Program Coordinators would be encouraged to continue to make contributions to the Program.

The meeting was recessed for lunch.

The meeting was reconvened by Dr. Newell, who asked the attendees to discuss the suggested new program areas.

Drs. Sugimura and Miller were called on to outline the research areas to be covered under the Carcinogenesis Program Area. Dr. Sugimura stated that he had previously discussed the research areas with Dr. I. Bernard Weinstein and had agreed to include the following:

A. **Cancer Carcinogenesis Program Area:**

1. Epidemiology
2. Chemical Carcinogenesis
3. Viral Carcinogenesis
4. Genetics and Molecular Oncology

During the discussions between Drs. Sugimura and Weinstein, it was agreed that Radiation Biology could be included under Genetics and Molecular Oncology.

Dr. Sugano suggested that instead of using the term "sub-areas" for the four categories, they should be called "projects" or "main interests."

Then, Drs. Terry and Yamamura discussed the main interests or research areas to be included under Biology and Diagnosis:

B. Biology and Diagnosis Program Area:

1. Cellular Biology
2. Molecular Biology
3. Immunology
    a. Biology
    b. Genetics
    c. Preclinical Immunotherapy
4. Diagnosis
    a. Automated Cytology
    b. Development of New Techniques

The discussion among the participants centered on matters of overlap between molecular biology versus genetics and molecular oncology. It was suggested that research on cell membrane, biology of normal and abnormal cells, cell differentiation, alteration of gene expression, and other basic research areas could be included under Molecular Biology.

Dr. Terry expressed his opinion that conceptually Biology and Diagnosis should include areas mostly related to fundamental research and not include molecular biology as related to carcinogenesis.

Drs. Sugimura and Newell agreed that there may be some overlap between the two program areas, but it may not be cumbersome to have intentional overlap with different emphasis on specific topics of research areas.

Drs. Carter and Sakurai discussed the Treatment Program Area. Dr. Carter stated that after much thought and discussion with Dr. Sakurai and others, it has been decided to have treatment modality and disease coordinated. The following format or outline was discussed:

C. Treatment Program Area

Modality Oriented

1. Chemotherapy (including new drugs, clinical trials, and drug development)
2. Radiation (High LET Radiation, Radiation Oncology, Hyperthermia, and New Developments)
3. Immunotherapy

Disease Oriented

1. Stomach Cancer
2. Lung Cancer
3. Breast Cancer
4. Bladder Cancer

During the discussion, the necessity of having a "working group" in each new program area was pointed out. Although the Program Area Coordinators have the primary responsibility for program planning in their own area, they may have a group of principal advisors which may act as an informal working group on an ad hoc basis in identifying projects or main interests and in working out plans for implementation for the Program Area.

Drs. Newell and Sugano then discussed the Interdisciplinary Program Area. It was recommended by Dr. Newell that this program area will use the Joint Steering Committee, including the JSPS and NCI staff, as the "working group." The following items or subject areas will be covered:

D. Interdisciplinary and Program Coordination:

1. Overall coordination of above three program areas
2. Consideration of new programs or special areas of interest
3. Sponsoring of interdisciplinary sessions
4. Organ sites.

The sponsoring of interdisciplinary sessions was strongly recommended by Dr. Yamamura, since Lung Cancer Diagnosis and Treatment depend on interdisciplinary work in such areas as Cell Diagnosis, Early Diagnosis, and Staging of Treatment.

After a brief recess, discussion was held on the Annual Joint Meeting of the NCI-JSPS Scientific Group, to be held in Japan on October 31 and November 1, 1978.

It was agreed that the JSPS and the NCI would send invitation letters to the Program Coordinators. At the meeting, the Annual Reports will be presented with a summary of the activities and accomplishments of the First Five-Year Program in each of the program areas. This phase will be considered during the first one and one-half days.

On the afternoon of the second day, the Joint Steering Committee will make a presentation of the program planning and structure for the Second Five-Year Program.

It was agreed that the Reports for 1978 together with the two published biennial Progress Reports will substitute for the five-year report of the Program.

The meeting was adjourned at 5:15 p.m. Mr. Amagi, Director-General, JSPS, graciously hosted a delightful dinner for the U.S. Delegation.

On June 3, 1978, at 9:30 a.m., Dr. Sugano reconvened the meeting. He summarized the discussions and the general agreements on the program areas. It was agreed that special appreciation would be expressed to the current Program Coordinators at the Fifth Annual Joint Meeting.

Mr. Soda presented the Proposed Plan for the Second Five-Year Program, which outlines a five-year plan on the basis of the agreements reached so far on the restructuring of the Program. He stressed that, if such a document would be agreed upon, it would be useful not only for the people interested to get a general idea of the Program, but also for the JSPS to submit the budget request for continuing the Program into the second five-year period. The Joint Steering Committee reviewed the Proposed Plan paragraph by paragraph for editing and made necessary modifications. The modified text is attached to the Minutes for reference.

It was stressed by everyone that the Joint Steering Committee will take on the responsibility of establishing program policy and providing general program planning. It was decided to hold the next Joint Steering Committee Meeting in San Francisco, California, in May 1979, possibly at the Northern California Cancer Program Headquarters in Palo Alto.

In order to stimulate scientific discussion at the Steering Committee meetings, it was agreed by Dr. Newell that special scientific sessions should be organized to review one of the program areas and to learn more about the state-of-the-art and research in the program area. It would be appropriate to invite special participants to these scientific seminars.

Mr. Soda thanked all the participants attending this meeting. Drs. Sugano and Newell also expressed their appreciation for the contributions each of the attendees made at the meeting.

The meeting was adjourned at 11:35 a.m.

The NCI Delegation hosted a buffet luncheon in appreciation of the hospitality extended by the Japanese Delegation.

Respectfully submitted,

Robert R. Omata, Ph.D.
Executive Secretary
U.S.-Japan Cooperative Cancer
Research Program

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RECORD OF THE
FIFTH ANNUAL JOINT MEETING

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FIFTH ANNUAL JOINT MEETING U.S.-JAPAN COOPERATIVE CANCER RESEARCH PROGRAM

Tokyo, Japan

October 31 and November 1, 1978

AGENDA

October 31

9:30 a.m.	OPENING SESSION	
	Opening Remarks	**Dr. Haruo Sugano,** Chairman JSPS Scientific Group
	Remarks	**Dr. Guy R. Newell,** Chairman NCI Scientific Group
	Welcoming Remarks	**Mr. Saburo Kasagi,** Executive Director, Japan Society for the Promotion of Science
	FIRST SESSION	**Dr. Haruo Sugano,** Chairman
9:50 a.m.	Report of the Chemical Carcinogenesis Program Area	**Dr. I. Bernard Weinstein** **Dr. Takashi Sugimura**
10:20 a.m.	COFFEE BREAK	
10:40 a.m.	Report of the Cancer Virology Program Area	**Dr. Yohei Ito**
11:10 a.m.	Report of the Cancer Immunology Program Area	**Dr. William Terry** **Dr. Yuichi Yamamura**
11:40 a.m.	Report of the Cancer Chemotherapy Program Area	**Dr. Stephen K. Carter** **Dr. Yoshio Sakurai**
12:10-2:00 p.m.	LUNCH	
	SECOND SESSION	**Dr. Guy R. Newell,** Chairman
2:00 p.m.	Report of the Analytical Epidemiology Program Area	**Dr. Robert W. Miller** **Dr. Takeshi Hirayama**
2:20 p.m.	Report of the Breast Cancer Program Area	**Dr. Nathaniel I. Berlin** **Dr. Haruo Sugano**
2:40 p.m.	COFFEE BREAK	

October 31 (continued)

3:00 p.m.	Report of the Cytology Program Area	**Dr. Chester Herman** **Dr. Kiyoji Kimura**
3:30 p.m.	Report of the Urinary Bladder Cancer Program Area	**Dr. George T. Bryan** **Dr. Osamu Yoshida**
3:50 p.m.	Report of the High LET Radiation Therapy Program Area	**Dr. Glenn E. Sheline** **Dr. Akira Tsuya**
4:10 p.m.	Report of the Lung Cancer Program Area	**Dr. Oleg S. Selawry** **Dr. Yuichi Yamamura**
4:30 p.m.	Report of the Metastasis Program Area	**Dr. Philip G. Stansly** **Dr. Haruo Sato**
5:00 p.m.	Adjournment	
6:30 p.m.	Reception in honor of the American Delegation, hosted by the Japan Society for the Promotion of Science	
November 1, 1978	BUSINESS MEETING	
9:00 a.m.	Report on the Second Joint Steering Committee Meeting June 2 and 3, 1978	**Dr. Guy R. Newell** **Mr. Kichimasa Soda,** Co-Chairmen
	Discussion of Modification and Restructuring of the Program	
	Review of the Second Progress Report	
	Preparation of the Final Annual Report	
11:15 a.m.	Joint Steering Committee Meeting	**Dr. Haruo Sugano** **Dr. Guy R. Newell** Co-Chairmen
	Closing Remarks	**Dr. Guy R. Newell** **Dr. Haruo Sugano**
12:30 p.m.	Adjournment	
	Luncheon in honor of the Japanese Delegation hosted by the NCI	

Co-Chairmen:
Dr. Haruo Suqano
Dr. Guy R. Newell

MINUTES OF THE FIFTH ANNUAL JOINT MEETING

Tokyo, Japan

October 31 and November 1, 1978

The meeting was called to order at 9:30 a.m. on October 31, 1978, by Dr. Haruo Sugano, Chairman, Japan Society for the Promotion of Science (JSPS) scientific group. Dr. Sugano expressed his pleasure in welcoming all of the participants. He also expressed the appreciation of the Joint Scientific Group to the Drafting Subcommittee for compiling and publishing the Second Progress Report (1976-1977) of the U.S.-Japan Cooperative Cancer Research Program, which was distributed to each of the participants.

Dr. Sugano then introduced the members of the Japanese Delegation. He stated that this meeting culminated the first five years of the Agreement for Cooperation in Cancer Research between the Japan Society for the Promotion of Science and the National Cancer Institute (NCI). He was personally pleased with the excellent results of the past five years of the Program and with the remarkable productivity and cooperation among the Program Coordinators and the numerous participants. From a scientific viewpoint, the Program contents have been excellent and the harvest of information and resulting collaboration have been extremely fruitful. He expressed his heartiest appreciation to the Program Coordinators for their concerted effort during the past five years of the Program.

Dr. Sugano stated that the Joint Steering Committee met in June 1978, to discuss the restructuring of the Program for its second five-year term. The new proposal for the Program will be presented during the Business Meeting for full discussion by the Joint JSPS-NCI Scientific Group. During this meeting the various program areas will be assessed and reviewed in the context of the past five years of program activities. Future program planning will also be discussed.

Dr. Sugano was delighted to announce that Dr. Takashi Sugimura was named by the Emperor of Japan to receive the august medal of the Order for Cultural Merit on National Culture Day, November 3, 1978, for his contribution in research in biology and medicine. The award is the highest national award given to outstanding scientists and academicians. All the participants joined in congratulating Dr. Sugimura.

Dr. Guy R. Newell, Chairman, NCI Scientific Group, responded by thanking the Japanese Delegation for the warm welcome and expressed his pleasure in visiting Japan again. He especially thanked the Japan Society for the Promotion of Science for the support given to the Program and also for arranging this meeting at the New Otani Hotel.

Dr. Newell extended warmest greetings to the participants from Dr. Arthur C. Upton, Director, NCI, and wished them all a successful and enjoyable meeting. He then introduced the members of the U.S. Delegation.

Dr. Newell extended his personal congratulations, on behalf of the U.S. Delegation, to Dr. Sugimura for the honor bestowed on him by the Emperor of Japan and the Japanese Government.

Mr. Saburo Kasagi, Executive Director, JSPS, delivered a welcoming address to the participants and thanked them for their contributions in establishing an excellent program.

Mr. Kasagi spoke as follows:

"On behalf of the Japan Society for the Promotion of Science, I want to thank you for attending the Fifth Annual Joint Meeting of the U.S.-Japan Cooperative Cancer Research Program.

Five years have passed, as you know, since this Program was launched in May 1974, when the representatives of the NCI and the JSPS met in Hawaii and signed the Agreement for Cooperation in Cancer Research between the two sponsoring agencies.

During these five years, joint scientific activities in 11 program areas have been largely developed in the form of scientific seminars, exchange of scientists, and exchange of materials and information. Many scientists of both countries have participated in the Program and conducted fruitful research activities.

In particular, I would like to point out that, besides accumulating knowledge on cancer and improvements in techniques resulting from joint scientific activities, the Program has had a great impact among scientists of both countries engaged in cancer research as a whole. Namely, the Program has increased the mutual sharing of each other's knowledge by means of bringing together varying viewpoints and methods from scientists of both countries which have had significant achievements in the field of cancer research. Moreover, the Program has contributed to the advancement of cancer research by means of scientific efforts to gain new knowledge and findings.

I think that we owe much of the success of the Program during the first five years to scientific endeavors and collaborations of the Co-Chairmen, Dr. Newell and Dr. Sugano, the coordinators of the program areas, and participating scientists, as well as Dr. Omata of the NCI. I would like to express our heartiest appreciation to these people.

According to the Agreement for Cooperation in Cancer Research between the NCI and the JSPS, the Agreement will be evaluated for renewal every five years. In this relation I want to report to you that the outline of the Second Five-Year Plan has been prepared by the efforts of the Joint Steering Committee. You will see the outline in the file of documents of this meeting, and the materialization of the plan is now under way.

The JSPS, jointly with the NCI, wants to implement the Second Five-Year Plan based on the achievements of the first five years of the Program. Your cooperation in this matter will be highly appreciated.

Finally, I would like to tell you about a happy event, and share my delight with you. Dr. Takashi Sugimura, an influential member of the U.S.-Japan Cooperative Cancer Research Program, will receive the Order for Cultural Merit, the highest national award given this year by the Japanese Government. We would like to share the delight with all of you and to cordially congratulate Dr. Sugimura on the award."

Drs. Sugano and Newell expressed their gratitude to Mr. Kasagi and the JSPS for the sponsorship of the U.S.-Japan Cooperative Cancer Research Program. Dr. Newell also expressed appreciation to Mr. Kichimasa Soda, JSPS, and Dr. Robert R. Omata, NCI, for their contributions to the administration of the Program.

Mr. Soda reported that the Second Progress Report was finished and published with the fine cooperation and work of the Joint Drafting Committee. The members of the committee were Drs. Yoji Ikawa, Takashi Hirayama, Ms. Yuko Kitamura Furukawa, Drs. Chester J. Herman, Glenn E. Sheline, and Robert R. Omata.

Mr. Soda reported that the Japanese Delegation and the JSPS would host a reception on October 31, 1978, at the Kasumigaseki Building in honor of the U.S. Delegation. A motor bus would provide transportation at 6:00 p.m. from the lower lobby of the hotel.

Dr. Omata announced that the Japanese Delegation would be honored at the buffet luncheon in the Sky Lounge at 12:30 p.m. on Wednesday, November 1, hosted by Dr. Newell, on behalf of the National Cancer Institute.

In order to complete all of the business in time, it was agreed that the Wednesday session would commence at 9:00 a.m.

CHEMICAL CARCINOGENESIS PROGRAM AREA

Dr. Sugano, as Chairman of the morning session, called on Drs. I. Bernard Weinstein and Takashi Sugimura to give their presentation for the Chemical Carcinogenesis Program Area.

Dr. Weinstein stated that it was a great pleasure to be in Japan again and to renew acquaintanceship with the Joint Scientific Group. He was pleased to see Drs. Robert Miller and William Terry again after their visit to the People's Republic of China last Fall.

He reported on the successful meeting of the past year on the "Role of DNA Repair and Misrepair in Radiation and Chemical Carcinogenesis," held in Kyoto, Japan, in December 1977. The subject of the meeting was an in-depth view of DNA repair and misrepair caused by radiation and chemical carcinogens. The meeting was a success with a great deal of exchange of information. The workshop was held jointly with the First Radiation Biology Center International Symposium entitled "Molecular Mechanisms and Genetic Factors in Radiation Carcinogenesis." Summaries of the individual presentations were included in the Annual Report.

A brief report was given on each of the exchange scientists, sponsored under the Chemical Carcinogenesis Program Area.

The exchange of protease inhibitors provided by Dr. Hamao Umezawa and the JSPS has been an extremely valuable adjunct to the Program. The use of protease inhibitors has opened up and stimulated a new area of research in cell biology and the study of the role of proteases in mutagenesis, carcinogenesis, and tumor promoters. It was agreed that a letter of appreciation from the JSPS and the NCI be sent to Dr. Umezawa for providing the materials and to Dr. Walter Troll for his services in providing samples to American and other foreign investigators interested in the inhibitors as research reagents.

Drs. Sugimura and Weinstein stated that the activities of the past year have been very productive and have established several collaborative studies, as well as stimulating warm and mutually beneficial relationships between scientists in Japan and the U.S. Dr. Sugimura made additional comments on the future program plans in the area of carcinogenesis, with a conference on "Carcinogenesis and Tumor-Host Relationships" being tentatively scheduled for March, 1979, in Honolulu, Hawaii. Several other proposed meetings or workshops were briefly mentioned. Plans were discussed on the pending exchange of scientists.

Drs. Philip Stansly and Haruo Sato stated that brief reports were very recently given at the Metastasis meeting in Nara, Japan, on the possible role of protease inhibitors in the therapy of micrometastasis. The mechanism of action and a joint study on use of a model system to study the role of protease inhibitors were discussed.

CANCER VIROLOGY PROGRAM AREA

Dr. Yohei Ito was called on to present the report for the Cancer Virology Program Area. Dr. Ito stated that it is most unfortunate that Dr. Robert McAllister was unable to attend the meeting and conveyed Dr. McAllister's sincere regrets and extended his best wishes to the participants.

Dr. Ito presented a brief summary of the activities of the past year and also summarized the main achievements of the Cancer Virology Program Area. There were several recent advances in cancer virology contributed by the participants at the series of workshops and symposia sponsored by the Program. New ideas and information on the role of adenoviruses were exchanged among the scientists from both countries. Several joint projects were initiated in viral genetics, molecular biology of viruses, and transformed cells.

The exchange of leading virologists led to the introduction of new techniques of studying cell transformation, and stimulated the exchange of new data on cell transformation and genetics of viruses. In total, the past five years of cooperation have proved to be extremely informative and productive. Dr. Ito reiterated that excellent opportunities are available to continue the dialogue that has been established and to take full advantage of these past and present contacts. He stated that he is very hopeful that cooperation will continue to flourish during the next five years.

CANCER IMMUNOLOGY PROGRAM AREA

The Chairman called on Drs. William Terry and Yuichi Yamamura to report on the Cancer Immunology Program Area.

They reported that the past year's activities were highly productive. A workshop on the "Immunological Xenogenization of Tumor Cells" held in Sapporo, Hokkaido, June 1978, was an important dividend from the past activities of the Cancer Immunology Program Area, although the workshop was not directly supported under the U.S.-Japan Cooperative Cancer Research Program.

A recent meeting on "Immunology and Cancer" was held in Maui, Hawaii, in September 1978. The main subjects of the meeting were experimental tumor immunology and human tumor immunology. The general discussions were held on broader areas of basic tumor biology and immunology. The proceedings of the meeting will be published in the near future. It was generally agreed that the future direction of this program area will put some stress on basic tumor immunology and cell biology, as well as clinical research.

The accomplishments of the program area during the past five years have been very significant, resulting in the establishment of valuable interaction among the participating scientists and the exchange of new information on immunology and immunotherapy from both countries. The Program Coordinators have acted as effective conduits or sources of information, disseminating the information to scientists of Japan and of the United States.

During the ensuing discussions among the participating members, the subject of preclinical and clinical trials on cancer immunotherapy was brought forward. The Japanese scientists have made considerable advances in investigating the immunopotentiating factors in BCG cell-wall skeleton as well as in cell-wall of *Nocardia rubra*. There is a great deal of basic immunology and immunochemistry to be accomplished before preclinical and clinical research can be effectively initiated.

It is the hope of the Program Coordinators that greater advances will be made in cancer biology and cancer immunology during the next five years of the Program.

CANCER THERAPY PROGRAM AREA

Drs. Stephen Carter and Yoshio Sakurai were asked to present the report for the Cancer Therapy Program Area.

Dr. Carter began by stating that there are several cooperative projects in clinical research, not supported by the U.S.-Japan Program, but initiated through the contacts and interactions promoted by the U.S.-Japan Cooperative Cancer Research Program. The most prominent project is the Gastric Cancer Therapy Project between a group of Japanese investigators and the Northern California Oncology Group.

It was reported that the presentations given at the symposium on anti-tumor antibiotics held in San Francisco, California, in May 1977 are being published in *Recent Results in Cancer Research* by Springer-Verlag. Also, the proceedings of the symposium on the methodology of Phase I and Phase II studies held in June 1978 will be published in the new journal *Cancer Chemotherapy*.

The activities during the past year have been extremely productive, particularly the exchange of information on the new advances in drug therapy using newly developed analogues of bleomycin, fluoridated pyrimidines, and nitrosoureas. There has been extensive exchange of clinical data on new drugs, such as macromycin and bestatin.

The past two years have been particularly informative in studying the treatment of gastric cancer under the Joint U.S.-Japan Cooperative Cancer Research Program. This joint effort has set the stage for other cooperative studies.

The Cancer Therapy Program Area is planning a meeting on recent advances in cancer treatment in San Francisco in May 1979. There has been renewed interest in mitomycin-C and in the advances in uterine cervical cancer treatment. Plans are being made to publish the proceedings.

Drs. Carter and Sakurai stated that excellent communication between clinical investigators from both countries and a tremendous amount of activity and interest have been stimulated by the Program.

Dr. Sakurai reiterated the importance of this Program during the past five years in initiating a number of joint symposia and establishing new cooperative projects. He hoped that the next five years will permit the concentration of effort on several joint projects and will provide impetus in the development of new anticancer drugs. He stated that the original cooperation on screening new drugs between the U.S. and Japan began in 1962 through the efforts of the late Dr. Tomizo Yoshida and Dr. Kenneth Endicott. This current Program has provided the necessary mechanisms for greater cooperation in cancer therapy. Dr. Sakurai hopes that the next five years will provide opportunities to extend the investigations in clinical trials, combined modality, clinical pharmacology, and drug toxicity studies.

The problem of the mutagenicity of anticancer drugs was discussed, particularly the possibility of altering the mutagenicity and toxicity of drugs by structural changes and producing analogues of currently used cancer drugs.

ANALYTICAL EPIDEMIOLOGY PROGRAM AREA

Drs. Robert Miller and Takeshi Hirayama reported that the Analytical Epidemiology Program Area sponsored a very informative and successful conference on "Biostatistics in the Study of Human Cancer" at the Radiation Effects Research Foundation in Hiroshima, Japan, in May 1978. The conference was a bilateral effort to stimulate and encourage the interaction of statisticians and physicians in seeking a fresh view on the use of medical statistics in relation to studying the epidemiology of cancer. About fifty scientists and physicians from both countries attended the conference. The interaction among the participants was excellent. The proceedings of the conference will be published in the near future.

The activities of the past five years of the Program have been very productive in terms of the exchange of scientists and the extensive exchange of epidemiological, environmental, and demographic information, as well as the exchange of geographic maps on cancer "hot spots." The cooperative studies produced two publications on the "Comparative Epidemiology of Cancer in the U.S. and Japan: Mortality and Morbidity." The Coordinators stated that future plans are to develop further the interactions between biostatisticians and physicians, to study the epidemiology of cancer, and to coordinate closer cooperation between the fields of epidemiology and carcinogenesis. The study of risk factors, particularly the relation of smoking, diet, and environment to cancer, is a very important aspect of the two fields of cancer research.

Dr. Oleg Selawry suggested that the incidence and prevalence of lung cancer could be a good tool for the study of environmental factors. Dr. Hirayama stated that epidemiological studies on the lung cancer cell types can be of great importance in studying risk factors. It was also reported that the National Academy of Sciences (United States) is sponsoring a conference on the toxicology of common substances and the information from this conference could well provide valuable clues to the relation of dietary and nutritional factors to cancer.

Dr. Weinstein reported that in the United States efforts have been made in evaluating occupational factors. Dr. Hirayama reported that there are several sources of information and statistics in Japan on occupational hazards and cancer. Presently there is a Japanese study on the asbestos problem. In addition, he reported that many mutagenic agents have been found in the environment and that these were being studied. Dr. Miller also reported that suspected carcinogenic factors found in vegetable pickles made in China were obtained and that this material was being investigated by Dr. Sugimura and his group for mutagenicity and carcinogenicity.

BREAST CANCER PROGRAM AREA

Drs. Nathaniel Berlin and Haruo Sugano presented their report on the activities of the Breast Cancer Program Area.

A very successful conference on "Hormone Receptors and Breast Cancer" was held in March 1978 in Hawaii, when over fifteen scientists from Japan and the U.S. discussed the role of hormones and receptors in human breast cancer and basic studies on endocrine therapy in breast cancer. It was evident from the discussions that Japanese scientists have made considerable progress in the hormone receptor field during the past three years since initiating studies on the comparison of population and the incidence of breast cancer in the two countries. The proceedings of the conference were recently published as one of the series in *Progress in Cancer Research and Therapy* by Raven Press of New York.

During the year, an exchange scientist from the Center for Adult Diseases, Osaka, Japan, visited several American cancer centers to discuss the possibility of organizing a joint workshop on the treatment of breast cancer. It was tentatively agreed to convene the workshop in Japan or in the U.S. sometime during the Spring of 1979.

The past five years of the Program have been extremely effective in exchanging information on the nature of breast cancer in both countries, the difference in the incidence of breast cancer, and the treatment of breast cancer. Also, information was exchanged on the detection and treatment of breast cancer on a national scale in both countries.

Several exchanges of personnel have made it possible to initiate collaborative efforts. It is anticipated that other cooperative projects will be established in the coming years. Leading Japanese scientists will be invited, on a continuing basis, to participate in the NCI sponsored Breast Cancer Task Force and to exchange information.

CYTOLOGY PROGRAM AREA

Drs. Chester Herman and Kiyoji Kimura presented their report for the Cytology Program Area.

They reported that there had been significant accomplishments achieved in automated cytology research since the cooperation was initiated. During the past five years, several joint workshops were organized, and the exchange of scientists proved to be very productive. Through this program, each side was able to gain extensive knowledge of the systems used in automated cytology in both countries. Collaboration in comparing the fluid analytic system versus the image processing system was accomplished. Through the cooperation of individuals and various research centers, research information came to fruition by comparing the same specimens using the different systems.

The capabilities of the image processing system and the flow system have been developing at a rapid pace through this cooperative effort. The technological aspects of automated cytology have reached a stage where the systems could be used for clinical application. Some of the new areas in which the systems may be of considerable utility would be in studies of white blood cells, differential blood counts, cytoplasmic studies of normal and tumor cells, cytotoxicity studies, and cellular immunology.

In the future, collaborative studies on cytology, cancer detection, and diagnosis will continue between the two countries in order to eliminate duplication of effort and waste of resources.

BLADDER CANCER PROGRAM AREA

In giving their report, Drs. Osamu Yoshida and George T. Bryan expressed their gratitude and appreciation to the Joint Scientific Group for the opportunity to work together in developing and coordinating the joint effort between Japan and the U.S. National Bladder Cancer Program. The bladder cancer programs in each country were in different stages of development; however, considerable interest was evident at the outset. The program was able to hasten the merging of the divergent interests in both countries in attempting to encourage urologists and other clinicians to engage in cancer research and basic biomedical research. The NCI sponsored National Bladder Cancer Program has been very effective and has encouraged Japanese clinicians and reseachers to participate in the workshops and conferences organized by the U.S. National Bladder Cancer Program.

As a result of joint participation in the Bladder Cancer Program and the exchange of scientists and information, several cooperative projects have been developed and are strong viable joint programs. The joint meeting in Florida in December 1978 will provide a forum to develop future joint studies. In recent years there has been considerable interest in the possible role of saccharin and nitrosamines in the causation of bladder cancer. These controversial issues will be discussed and future joint studies may be planned.

Dr. Newell congratulated Drs. Yoshida and Bryan for their efforts in developing an excellent program after a late start. The program area progressed very rapidly and he stated that he hoped that the high level of activity will be sustained in the future.

Drs. Bryan and Yoshida reported that there is still much to be learned in the area of bladder cancer, and the difference between the Japanese and American populations should be further explored. The subject of promoters is very important, and they hope to devote more effort to identifying and reclassifying the promoters.

HIGH LET RADIATION THERAPY PROGRAM AREA

Drs. Glenn Sheline and Akira Tsuya reported that the High LET Radiation Therapy Program began in late 1975 and the program has rapidly developed into a very active one. Initially, the joint efforts were concerned with neutron studies and comparative measurements with teams of Japanese and American scientists.

The Program Coordinators reiterated that the joint cooperation was particularly productive with excellent relationships developed through joint investigations on basic and developmental problems. During the past year, the program has dealt with fast neutron radiobiology and radiotherapy. Also, joint studies have been initiated on clinical trials with particulate radiation. New areas of cooperation have been initiated on hypoxic cell radiosensitizers, hyperthermia, and intraoperative radiation therapy. As a result of earlier cooperation on particle radiation, new studies are being developed.

The program area is planning a large meeting in Kyoto in May 1979, in conjunction with the International Congress on Radiation Research to be held in Japan in May 1979.

In addition to the workshops and seminars sponsored under the program area, several Japanese participants were invited to attend and participate in the meeting of the United States

Committee for a Comprehensive Plan for Particle Radiation Therapy held in Philadelphia in June 1978

The exchange of scientists during the past four years has been particularly effective and productive in terms of the exchange of research information, as well as in conducting joint research studies.

LUNG CANCER PROGRAM AREA

Drs. Yuichi Yamamura and Oleg Selawry presented a brief summary of the joint meeting on "Multidisciplinary Treatment of Lung Cancer" held in February 1978 in Honolulu, Hawaii. The "Morphology of Pulmonary Neoplasms," as described in the Second Edition WHO Report, was discussed by two members of the WHO Committee. Then the subjects of immunotherapy of lung cancer, including microbial cell-wall skeleton vaccine therapy, surgical adjuvant treatment, and the present status of immunotherapy in Japan and the United States were discussed. Multidisciplinary treatment of small cell carcinoma and non-small cell cancer was extensively discussed by the participants. Adjuvant surgical treatment was discussed by two leading surgeons.

Progress of the program area over the past five years was discussed by the Program Coordinators. Initially, meetings were held on staging and morphology to coordinate compatible staging systems. The WHO classification of pulmonary neoplasms was discussed and fully accepted. Sessions on early diagnosis were extremely fruitful with Japanese specialists demonstrating the new fiberoptic bronchoscopes developed by Japanese investigators. Subsequent meetings on the multidisciplinary approach to the treatment of lung cancer have been particularly informative and productive in providing opportunities for clinical investigators from both countries to become aware of the current status of lung cancer treatment.

Plans are being developed to hold a conference on lung cancer treatment in Miami, Florida, in February 1979.

Inasmuch as cooperation has been established during the past years, joint programs will be developed for studying the prevention of lung cancer. Studies on diagnosis based on cell types will be continued. The principles of anti-carcinogenesis, such as the use of retinoic acid analogues and the vaccine produced from microbial cell-wall skeleton, will also be of considerable continuing interest and collaboration.

During the discussion it became evident that lung cancer has been increasing at an alarming rate, not only in the U.S. and Japan, but worldwide. There is growing interest in learning more about the causative factors.

METASTASIS PROGRAM AREA

Drs. Philip Stansly and Haruo Sato presented a report on the meeting on "Experimental Approaches to the Therapy of Micrometastases" which was held in Nara, Japan, just prior to this Joint Review Meeting. Several subjects discussed at the last meeting could lead to several interesting areas of collaboration. Topics were discussed such as the immunologic host factors; properties of metastatic cells, including cell membrane, and the differences in the enzymes in normal and tumor cells; the effect of glucose on potentiating drugs, delivery of antitumor drugs to tumor cells; and studies of models. The discussions were extremely informative and stimulating. The general conclusion of the meeting was that cancer cannot be conquered until the mechanisms of metastasis can be well understood and properly treated. The metastatic process is very important in several types of cancers, such as lung cancer.

There is much interest in metastasis research and more investigations must be accomplished to understand the location of tumor cells, transport lodgment of micrometastatic cells, vascularization of cells and tissue, and the formation of metastatic foci.

The Program Coordinators stated that, since a beginning has been made in the joint effort to study metastasis under the U.S.-Japan Program, interest among investigators should be sustained to maintain the momentum generated under this program.

The first day of the meeting was adjourned at 5:00 p.m. The Chairman announced that the Joint NCI-JSPS Scientific Group would reconvene at 9:00 a.m. on Wednesday, November 1, 1978.

The JSPS hosted a reception at the Tokai University Club at the Kasumigaseki Building beginning at 6:30 p.m.

Business Session

Drs. Haruo Sugano and Guy Newell called the meeting to order at 9:00 a.m.

Dr. Newell expressed the appreciation of the U.S. Delegation to Mr. Saburo Kasagi and the JSPS for hosting the reception at the Tokai University Club on October 31.

The minutes of the Joint Steering Committee Meeting, held in Tokyo on June 2 and 3, 1978, were presented to the Joint NCI-JSPS Scientific Group for discussion.

Dr. Newell stated that the intent of the Joint Steering Committee is to keep many of the present program areas functional as much as possible. The purpose of the new structure is to consolidate the eleven program areas into four large categorical program areas to meet the needs of the changing interests and new research areas now emerging. Under the new structure, Program Coordinators have been named for: (1) Carcinogenesis; (2) Biology and Diagnosis; (3) Treatment; and (4) Interdisciplinary Programs.

1. **Carcinogenesis:**
   Dr. Takashi Sugimura
   Dr. I. Bernard Weinstein

2. **Biology and Diagnosis:**
   Dr. Yuichi Yamamura
   Dr. William Terry

3. **Treatment:**
   Dr. Yoshio Sakurai
   Dr. Stephen Carter

4. **Interdisciplinary Programs:**
   Dr. Haruo Sugano
   Dr. Guy Newell

The Interdisciplinary Program and Coordination Area will in essence provide support for general coordination of the total Program and also meet the needs for the development of new areas of cancer research. The area will also provide support for exchanges, workshops, and conferences with strong interdisciplinary orientation or crossing over of two or more fields.

It has been agreed by the JSPS and the NCI that the Joint Steering Committee will act as the policy making body for the Program.

Drs. Newell and Sugano asked for discussion and opinions from the delegations. Mr. Kichimasa Soda stated that the JSPS was generally satisfied with the formation of the Joint Steering Committee and that the new approach or structure would be more flexible and add greater breadth to the Program contents.

Dr. Berlin asked whether the organ site programs would be considered under the Interdisciplinary Area. He stated that he would strongly recommend that Breast Cancer, Lung Cancer, and Bladder Cancer Programs be continued with other organ sites added as new programs as the needs demand.

Dr. Newell stated that the Joint Steering Committee felt strongly that the current structure of eleven program areas was cumbersome and somewhat restrictive in the attempt to begin new initiatives. He also stated that the new structure will need time to be implemented and that the JSPS needed prior planning for funding from sources within the Japanese Government. There is no wish on the part of the JSPS or the NCI to diminish the activities and the considerable progress that have been supported in the past; however, there will be greater need for forward planning to justify the budgeting and funding processes.

Mr. Soda and Dr. Newell stated that it will be necessary for program organizers and coordinators to submit proposals and plans rather early during the fiscal year. There will be a need for the newly designated Program Coordinators to submit plans for each year's activities, or at least some general outline or ideas.

In order to sponsor seminars, workshops, and conferences, the Program Coordinators will have to be contacted early by those who are planning to submit proposals for funding under the new structure. For instance, if a proposal for a Breast Cancer Treatment Workshop is received, the Joint Steering Committee will decide to have the workshop supported under the Cancer Treatment Program Area. Again, if the Bladder Cancer group wishes to organize a workshop on Etiology, Diagnosis, and Treatment of Bladder Cancer, the proposal will be referred to the Interdisciplinary Program Area.

Mr. Soda stated that there will be additional responsibilities for planning and organization placed on the Program Coordinators; therefore, it will be up to the Program Coordinators not only to provide planning but also to put plans into practice, maintaining contact with the JSPS and the NCI for budget purposes.

Under the current (First Five-Year Program) structure, Dr. Newell stated that subject matters were "locked into" the eleven designated Program

Areas and that each of the eleven areas felt there was responsibility to hold one meeting per year. Under the new program structure, it will be easier to combine two program areas (e.g., immunology and cytology) to hold a workshop or a meeting to cover both areas.

Dr. Yoji Ikawa reiterated that under the current system, the program content was distinct and it was the responsibility of the Co-Program Coordinators to plan their respective program area.

Mr. Soda stated that under the new structure there will be Program Coordinators selected for four large program areas instead of eleven program areas. The newly appointed Program Coordinators will have greater responsibility and will need to be more aware of the different research areas.

Dr. Ikawa recommended that for the Japanese the present eleven coordinators could remain as participants and an advisory or program body could meet to advise the JSPS. It was suggested that the four newly appointed Program Coordinators could use other consultants or "principal advisors" on a semi-permanent or ad hoc basis for advice.

Dr. George Bryan asked if the present JSPS-NCI Scientific Group would be dissolved. Dr. Newell stated that it has been in existence for five years and a change was needed and there should also be "turnover" of program areas. Dr. Newell further stated that he and others have been greatly appreciative of everyone's efforts in the past. Mr. Soda joined Dr. Newell in expressing their hopes that the present members of the JSPS-NCI Scientific Group will continue to participate in the Program as consultants to the new Program Coordinators or as organizers of workshops and conferences. They both praised the work of the present members.

Dr. Yuichi Yamamura asked what will happen to the current plans for meetings. Dr. Newell and Mr. Soda stated that the Program will honor the present commitments already made for the support of exchanges and meetings.

Dr. William Terry asked if the new structuring would increase or diminish funding. Mr. Soda responded by stating that the JSPS has plans for an increase of funds, but he is optimistic of at least a leveling for the present. It has been estimated that the JSPS and the NCI are each providing approximately $250,000 per year.

Dr. Oleg Selawry stated that the Program has acted as a catalyst and has stimulated new projects and collaboration. Dr. Bernard Weinstein stated that the Program has provided "seed money" for new exchanges and meetings. Several of the tangible and intangible benefits from the Program were discussed.

Dr. Selawry further stated that the Program Coordinators have established a great deal of mutual respect and trust for each other and smooth cooperation has resulted. He recommended that these intangible investments be preserved in the future.

Dr. Ikawa asked if the new Program Coordinators will include others who have new ideas and new advances. He recommended that each program area should have some type of a "working group" or an "advisory or consulting group."

Dr. Newell stated that all of us associated with the Program, presently and in the future, will need the support of everyone to make the Program functional. The next year will be a transitional period and he would like to see input from anyone who has been participating in the Program.

Dr. Yamamura asked about the opinion of the JSPS. Dr. Sugano stated that the plans are that the term of the present JSPS-NCI Scientific Group will end on March 31, 1979, and the new Program Coordinators will be appointed effective April 1, 1979. Each side will make recommendations for "principal advisor" or "working groups." He stated that the Japanese side has generally agreed to the new structure and that the transition period could create some problems.

Dr. Takashi Sugimura agreed with Dr. Weinstein that the Chemical Carcinogenesis or Carcinogenesis Program Area should be changed to the Etiology Program Area. During the past five years, the Chemical Carcinogenesis Area had covered a rather broad area of cancer research besides chemical carcinogenesis. The new Etiology Program Area will present opportunities to provide coverage for environmental carcinogens, epidemiology, viral oncology, radiation biology, and other research areas.

He further stated that new needs and research advances must be met by a more flexible and broader program structure. There may be some good and some bad experiences, but the Program must be in a position to be more responsive to new demands. He believes that under the new program structure, the JSPS will have more justification to obtain government funds. He further stated that the current Program has been excellent in furthering goodwill, mutual trust and respect, and very smooth collaboration among all the program areas.

Dr. William Terry stated that the Joint Steering Committee has a good mutual agreement in their perception of restructuring the Program, thereby strengthening and improving the Program.

Drs. Ikawa and Weinstein suggested that progress reports from the exchange of scientists would be an excellent device to evaluate the effectiveness of the Program. The report forms will be mailed by the NCI to the Program Coordinators so that they may be integrated into the future annual reports. It was agreed that the draft of the annual report would be compiled by the NCI summarizing the reports presented at this meeting, and that it would be published by the JSPS in the Spring of 1979.

Drs. Newell and Sugano recommended that letters of appreciation be sent from the JSPS and the NCI to Dr. Hamao Umezawa for his contributions to the Program and for the supply of protease inhibitors he provided for research purposes. The inhibitors have added a new area of interest in the field of cellular and molecular biology. Also a letter of appreciation will be sent to Dr. Walter Troll for his services in distributing the protease inhibitors to American and other foreign scientists for research in cell biology.

Drs. Sugano and Newell reported that the Japanese Association for Cancer Research would like to publish a GANN monograph about the U.S.-Japan Cooperative Cancer Research Program, limited to twenty contributed articles on cancer research. It is planned to be a publication of scientific activities. Dr. Sugano invited all of the Program Coordinators to contribute articles for the publication. The proposed deadline for the manuscripts will be July 1979 for February 1980 publication.

Mr. Justin Bloom, Counselor for Science and Technology, American Embassy, Tokyo, Japan, reported that the Embassy judges the U.S.-Japan Cooperative Cancer Research Program to be one of the best cooperative scientific programs between Japan and the U.S. He stated that many scientists and lay persons do not know of the Program. He suggested that an article about the Program be published in *Science* or other widely read journals which have worldwide distribution. Dr. Newell reported that a brief article appeared in the *Journal of the National Cancer Institute* (JNCI) in February 1977.

Dr. Terry asked about the audience for the GANN monograph. Dr. Sugano stated that the monograph content would be targeted to the world scientific community, providing information on the Program as well as documentation of scientific progress and cooperation sponsored under the Program. Dr. Terry suggested that other participants in the Program, such as exchange scientists and participants at the workshops and seminars who are recognized authorities in their respective fields, should be invited to submit manuscripts. Dr. Sugimura stated that he is inclined to think that most scientists would rather publish primary papers in various journals and consider monographs and review articles as secondary publications. Monographs, in general, contain review articles which are usually of general interest.

Dr. Newell stated that he and Dr. Sugano are extending invitations to all of the Program Coordinators to submit manuscripts for the GANN monograph.

The meeting was adjourned at 10:40 a.m. by the Co-Chairman, with heartiest thanks to all the participants.

Respectfully submitted,

Robert R. Omata, Ph.D.
Executive Secretary
U.S.-Japan Cooperative
Cancer Research Program
National Cancer Institute

Co-Chairmen:
Dr. Haruo Sugano
Dr. Guy R. Newell

MINUTES OF THE JOINT STEERING COMMITTEE MEETING

Tokyo, Japan

November 1, 1978

The Co-Chairmen of the Joint Steering Committee, Drs. Haruo Sugano and Guy Newell, called the meeting to order at 11:05 a.m. The following members and observers were in attendance:

> Drs. Haruo Sugano, Yuichi Yamamura, Yoshio Sakurai, Takashi Sugimura. Mr. Saburo Kasagi, Mr. Kichimasa Soda, Drs. Guy Newell, Stephen Carter, William Terry, I. Bernard Weinstein and Robert Omata. The observers were Mr. Nagahide Onozawa, JSPS, and Dr. Donald Henson, NCI.

Drs. Weinstein and Sugimura began the discussion on the four new Program Areas:

1. Carcinogenesis
2. Biology and Diagnosis
3. Treatment
4. Interdisciplinary Program

It was recommended that the Carcinogenesis Program Area be changed to Etiology Program Area and include the sub-areas of: (a) Epidemiology, (b) Chemical and Radiation Carcinogenesis, (c) Viral Carcinogenesis, and (d) Genetics.

The subject of implementation of the newly structured program was brought up for discussion. Initially the Program Area Coordinators should plan for two or three meetings per year for each of the Program Areas. It was the general opinion of the group that there may be some difficulty in program planning for the first year. It will be necessary for each side to invite appropriate consultants or principal advisors for each of the Special Interests under the Program Areas.

Also, the problem of sponsoring a meeting which is among one of the current structures, for instance, metastasis, should have to be categorized under Biology and Diagnosis. Other examples are as follows:

1. Lung Cancer Treatment Meeting would be under Treatment Program Area
2. Bladder Cancer Meeting could easily be under Interdisciplinary as organ site and the meeting would deal with the multidisciplinary approach to cancer
3. Breast Cancer Treatment would be under Treatment Program Area.

A proposal for meetings from any scientist or investigator who wishes to organize a meeting under the U.S.-Japan Cooperative Cancer Research Program would have to have a co-organizer from the other side. The proposal could be sent to the Program Area Coordinator for his country or sent to the JSPS or the Office of International Affairs (OIA), NCI. It would be up to the JSPS or the NCI to notify the Program Coordinators and obtain a review or opinion on the worthiness and/or priority for sponsorship of the meeting under the appropriate program area.

Mr. Soda and Dr. Terry suggested that the responsibility for programming and planning would be that of the Program Coordinators. A procedure for referral by the JSPS and the OIA, NCI, can be established. This was agreed upon.

Dr. Weinstein asked if the organ sites will be limited to only four, such as stomach, lung, breast, and bladder. It was agreed that organ sites would be selected on an ad hoc basis under the Interdisciplinary Program Area. It was agreed that proposals on organ sites should be left open, depending on the main topic or topics which the organ site proposal would emphasize, such as chemotherapy of bladder cancer. It was generally agreed that topics on organ sites will be considered on a priority basis for support. It was also agreed that the Interdisciplinary Program Area will act as the "clearing house" for proposals on organ sites and possibly refer the proposal to the appropriate Program Area.

After considerable discussion, Drs. Sakurai and Carter agreed that Clinical Trials should be included under Treatment, in which the following research areas will be included:

Treatment:

1. Chemotherapy
2. Radiation Oncology
3. Immunotherapy
4. Combined Modality
5. Clinical Trials

The subject of selection of Principal Advisors was brought up for discussion. It was generally agreed that the Program Area Coordinators will have the prerogative of establishing ad hoc or semipermanent advisors to form a working group. The coordinators should have the freedom to select advisors on a one-time or continuing basis, according to their needs and requirements. The selection will remain an open policy. Some advisors may be invited on a one-year term basis.

Dr. Terry led a discussion on the possibility of a person, outside of the new structure, proposing a meeting or seminar. It will be possible for a potential proposer or organizer with a new idea to contact one of the advisors for his opinion and then refer the proposal to the Program Coordinator for a decision for support. Dr. Yamamura stated that he favored the procedures to have the Program Coordinators make the decision to support the meeting or exchange of personnel with consultation with an appropriate advisor. This procedure was agreed upon by all the Program Coordinators.

There was full agreement that the following structure of the Program Area will be estblished in 1979:

I. *Etiology*
   1. Epidemiology
   2. Chemical and Radiation Carcinogenesis
   3. Viral Carcinogenesis
   4. Genetics

II. *Biology and Diagnosis*
   1. Cellular and Molecular Biology
   2. Immunology
   3. Diagnosis

III. *Treatment*
   1. Chemotherapy
   2. Radiation Oncology
   3. Immunotherapy
   4. Combined Modality
   5. Clinical Trials

IV. *Interdisciplinary and Program Coordinators*
   1. Overall coordination of above three program areas
   2. Consideration of the new programs or special areas of interest
   3. Sponsoring of interdisciplinary sessions
   4. Organ sites

It was agreed that the First Joint Steering Committee Meeting be held in San Francisco, California, on May 24 and 25, 1979, following the Chemotherapy Review Meeting on May 21 to 23, 1979.

Finally, Dr. Donald Henson was asked to present a brief report on the possibility of a collaborative study on "Low Dose Radiation and Breast Cancer" between the National Cancer Institute (NCI) and the Radiation Effects Research Foundation (RERF) in Hiroshima, Japan. If the proposed collaboration is finally approved by the NCI and the RERF, the U.S.-Japan Cooperative Cancer Research Program would provide the "stamp of approval" and provide support for a limited number of personnel exchanges under the Interdisciplinary Program Area.

The meeting was adjourned at 12:30 p.m. The National Cancer Institute hosted the Japanese delegation and other members of the Joint Scientific Groups to a buffet luncheon.

Respectfully submitted,

Robert R. Omata, Ph.D.
Executive Secretary
U.S.-Japan Cooperative
Cancer Research Program
National Cancer Institute

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Mr. Iwao Abe
Research Cooperation Division

Mr. Shigeyuki Shimoda
Research Cooperation Division

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PLAN FOR SECOND FIVE-YEAR PROGRAM

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PLAN FOR SECOND FIVE-YEAR PROGRAM

Purpose

The U.S.-Japan Cooperative Cancer Research Program was initiated in 1974 between the National Cancer Institute (NCI) and the Japan Society for the Promotion of Science (JSPS), with a view to eventually conquering cancer, a common enemy of mankind. The United States and Japan respectively developed cancer research under different academic and cultural systems. Furthermore, cancers in the two countries show different characteristics from the viewpoint of geographic pathology. Special significance was mutually recognized of planned cooperation between the scientists of the two countries with such different backgrounds. The first five-year cooperative program comprised scientific seminars, exchange of scientists, and exchange of research materials and information, and covered eleven areas of cancer research.

The achievements during the first five-year period are described in detail in the First Progress Report (1974-75), the Second Progress Report (1976-77), and the Third Progress Report (1978). Notable progress was witnessed in the eleven areas of cancer research. Among the important achievements of the cooperative program are comparison of cancer patterns of the two countries, development and application of carcinogen and mutagen assay methods, introduction of new technology in cytology automation, high LET radiation, comparative study on new antitumor drugs, and the establishment of a fundamental basis of immunotherapy. The Program made it possible for a large number of cancer researchers of the two countries to be acquainted with each other through research and discussion. Such a personal contact is also a great achievement of the Program, which is intangible but highly stimulating for the progress of cancer research in the respective countries.

With these achievements and experience during the first five-year period, the Second Five-Year Cooperative Research Program will be started in 1979 to further the common purpose of diminishing disability and death from cancer.

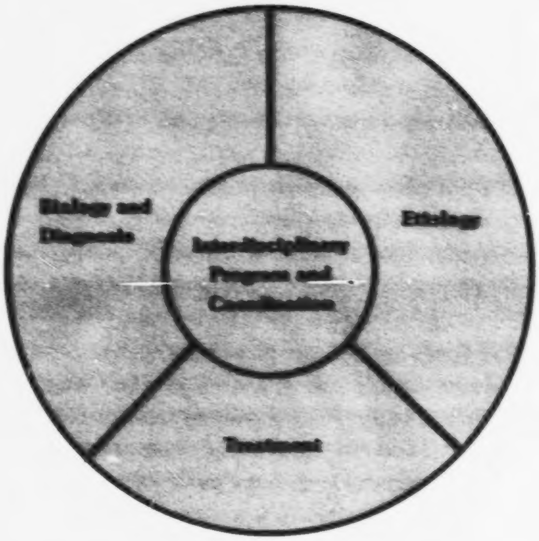
The main objectives are as follows:

1. To identify environmental and intrinsic carcinogenic factors and mechanisms through laboratory and epidemiological research in order to further the understanding of causes of cancer and means of its prevention.
2. To clarify the nature of cancer cells from the stand-point of cellular and molecular biology; to explore further the nature of fundamental immunologic processes that may determine host responses to cancer; and to develop new methods for the early diagnosis of cancer.
3. To develop new anticancer drugs, new developments in radiation oncology, new immunotherapeutic approaches, and combined modality studies most appropriate to specific disease sites. Collaborative trials will be undertaken to compare results in

both countries and to maximize the rapid accumulation of meaningful data. Disease sites to be emphasized include gastric cancer, lung cancer, breast cancer, and bladder cancer.

Areas for Cooperation

The following four major areas for cooperation will be newly established in place of the previous eleven areas, so as to give greater flexibility in carrying out cooperative research:



The Interdisciplinary Program and Coordination Area serves the functions of general coordination of the three program areas, consideration of new programs of scientific merit, and facilitation of interdisciplinary program areas of high priority and other organ sites.

The restructuring of the areas for cooperation is required by the present social needs of the two countries and recent cancer research progress in the world, as well as from the experience of the first five-year program.

Each area will have two coordinators, one appointed by each country. A number of areas of special interest may be identified for each area to indicate priority in the implementation of cooperative activities. These areas of special interest may change during the five years, depending on the scientific opportunity and new knowledge. Coordinators may appoint principal advisors to assist them in developing the areas of special interest as they evolve.

The areas of special interest are as follows:

I. *Etiology*
    Epidemiology
    Chemical and Radiation Carcinogenesis
    Viral Carcinogenesis
    Genetics

II. *Biology and Diagnosis*
    Cellular and Molecular Biology
    Immunology
    Diagnosis

III. *Treatment*
    Chemotherapy
    Radiation Oncology
    Immunotherapy
    Clinical Trials

IV. *Interdisciplinary Program and Coordination*
    Overall coordination of above three program areas
    Consideration of new programs or special areas of interest
    Sponsoring of interdisciplinary sessions
    Organ sites.

New Machinery for Implementation

1. The Joint Steering Committee Meeting as a policymaking group will meet at least once every year.
2. The Joint Steering Committee Meeting will discuss the following matters:
    - Policy matters concerning the U.S.-Japan Cooperative Cancer Research Program
    - Overall plan for the Second Five-Year Program
    - Annual program including scientific seminars, exchange of scientists, and exchange of materials and information
    - Matters concerning the coordination among the program areas for cooperation
    - Matters concerning inter/multidisciplinary programs
    - Evaluation and report of activities
    - Any other matters which need agreement between the NCI and the JSPS.

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3. Participants of the Joint Steering Committee Meeting will be the representatives and executive secretaries of NCI and JSPS and the program coordinators of the four areas. If deemed necessary, special guests may be invited to participate in the meetings as ad hoc members.
4. The agreements reached at a Joint Steering Committee Meeting will be effective as approved by both NCI and JSPS.
5. The NCI and the JSPS will maintain close contact by occasional meetings or correspondence to prepare for the Joint Steering Committee Meetings and to consult with each other in regard to the implementation of the cooperative program.

Types of Activity and Financial Responsibilities

Activities that will be supported by the NCI and the JSPS under this cooperative program are (1) scientific seminars, (2) exchange of scientists, and (3) exchange of materials and information. Each type of activity will be carried out as follows based upon the priority and availability of the funds:

1. **Scientific Seminars.** The NCI and the JSPS will support selected scientific seminars and workshops in fields that are rapidly developing or in need of development, on the basis of the proposals submitted by the coordinators of each area or by the principal advisors through the coordinators concerned, within the framework of the annual program approved by the Joint Steering Committee Meeting. The NCI and the JSPS will share the cost of these seminars including travel, living allowance, and other expenses of their own participants.

2. **Exchange of Scientists.** The NCI and the JSPS will support the exchange of a limited number of American and Japanese scientists either for a short-term period or a long-term period, on the basis of the proposals submitted in a similar way as prescribed in the preceding paragraph. Such exchange is not intended for training but for promoting cooperation. The NCI and the JSPS will pay the travel and living allowance of their own participants.

3. **Exchange of Materials and Information.** The NCI and the JSPS may promote and develop the exchange of materials and information between the scientists and clinical investigators in the two countries and share the cost of such exchanges.

4. **Direct Collaboration.** As an outgrowth of seminars and the exchange of scientists, direct collaborative activities may develop and these activities will be facilitated.

5. **Others.** The Program will not fund research projects or activities other than those listed above.

Procedure for Program Preparation

1. Within the framework of the overall plan of the Second Five-Year Program, the coordinators of each area will prepare a proposed annual program plan of their area, in consultation with the principal advisors, if necessary. Such a program plan should indicate priority subject matters of that program area as well as the proposed number of projects for each type of activity.

2. These proposed program plans will be submitted to the Joint Steering Committee through the respective implementing agencies. The Joint Steering Committee will consider these program plans as submitted and make recommendations.

3. Within the framework of the annual program plans considered by the Joint Steering Committee Meeting, the coordinators will prepare, in cooperation with principal advisors, specific proposals for each type of activity and submit them to the respective implementing agencies.

4. The implementing agencies will consult with each other and, if agreed, they will notify the coordinators concerned of their approval of the proposals, which then will be implemented.

5. For the first year of the Second Five-Year Program, a special procedure will be utilized by the NCI and the JSPS to facilitate the implementation of the cooperative program.

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